The oxygen necessary for this combustion is furnished by the atmosphere. With every breath we take in oxygen, with every breath we give out carbon dioxide and water.

Thus we may compare the animal body to a heat engine. The fuel, the source of energy, is represented by food. The inlet for the draught of air and the outlet for the waste gases, the products of combustion, are both combined in one organ, the lungs, which we use to take in oxygen and give out CO_2 and water; and just as the coal used in engines has some incombustible constituents which remain as ash and have to be raked out, so there are parts of our food which the body cannot make use of, and which leave the body as excrementitious matter or fæces, having passed through the alimentary canal without at any time having formed part of the tissues. There are still two constituents of foodstuffs which have to be got rid of after the elimination of CO_2 and H_2O by the lungs—namely, the nitrogen and sulphur contained in the proteins. This function is served by the kidneys. The nitrogen is combined in the body with carbon and oxygen to form a substance called urea, and in this form is excreted by the kidneys, together with salts and water, as urine. The sulphur is oxidised to a sulphate, and in this form also appears in the urine.

We must mention here that water and salts are indispensable and invariable components of the food. Neither of these possesses any potential energy, but they are essential constituents of all living substances, and must be taken to replace the loss of them from the lungs, skin, and kidneys, the water formed in the body by the oxidation of the hydrogen of the foodstuffs being far too small to compensate this loss.

The income and output of the body may be arranged in the form of an equation—

$$\text{Food} + \text{oxygen taken up} = \text{fæces} + nCO_2 + nH_2O + \text{urea}\ \left(CO{<}^{NH_2}_{NH_2}\right),$$

and in the same way we may make an equation of the income and output of energy—

$$\begin{gathered}\text{Energy set free by burning of food to } CO_2,\ H_2O, \text{ and urea}\\ = \text{work done by body} + \text{heat given off.}\end{gathered}$$

The truth of these equations has been proved by many elaborate observations both on animals and men.

Thus from one point of view physiology may be regarded as the history of all the changes undergone by the food in its passage through the body, and the mechanisms by which its potential energy is transformed into the kinetic energy of the various vital manifestations.

But this analogy with the heat engine must not be pushed too far. In this the fuel, the source of energy, is always distinct from the machinery by which its energy is converted into work. In the body it is otherwise. The food that we take in is digested, assimilated, and built up to form part of the living framework of the body. This living stuff at the same time takes up oxygen, so that a molecule is formed containing all the elements necessary for evolution of energy. Under certain conditions the foodstuffs and the oxygen in the living molecule combine together, the unstable living molecule of high potential energy splitting up to form stable compounds with lower potential energy, a certain amount of energy in the form of heat or work being rendered kinetic or actual in the process. So the changes that the foodstuffs undergo in their passage through the body may be divided into two main stages:

(1) *Assimilative or anabolic changes.*—The food that is absorbed from the alimentary canal, and the oxygen that is taken in through the lungs, are built up into and become actual constituents of the living protoplasmic molecule. These processes, which are spoken of under the term *anabolism,* are associated with evolution of very little energy; or it is possible that energy may become latent in the process, the building up being effected at the expense of some previously formed unstable compound.

(2) *Dissimilative or katabolic changes.*—These are the changes which are always associated with activity, that is, with the manifestation of some form of energy (heat, work, electrical change, etc.). The molecule of protoplasm breaks down, most of the atoms arranging themselves to form the stable compounds, CO_2, water, and perhaps urea, just as a molecule of nitro-glycerin when struck explodes with great evolution of heat, and with the formation of stable and more simple molecules. But in the living body the explosion is rarely (under physiological conditions) complete. There is always a remainder which does not undergo decomposition,

and which we endow with the attribute of *living*, since it possesses the power of self-restitution, and can take up foodstuffs and oxygen, and so build itself up again into the same unstable molecule as before, ready to break down in part and give rise to kinetic energy.

These changes of breaking down of a highly complex living molecule, with the evolution of energy, are spoken of under the general heading of *katabolism*.

Before treating these processes any further, we must pause awhile to consider the manner in which the body is built up, and what are the essential morphological characters common to all forms of life. This unity in the structural basis of all living beings will be seen better after a study of one of the simplest forms; and as a type of these we may take the well-worn example of the amœba.

This is a minute organism of variable size, found in stagnant water and in damp earth. If we examine it under the microscope we find that it consists of a small lump of transparent material, which can be shown by chemical tests to belong to the protein group of bodies. But it is distinguished from a mass of inert protein by the facts that it is able to ingest and digest food and build it up into its own substance, that it can move about from place to place, responds to stimulation by contracting up into a round ball, and has the power of reproduction by fission—that is, one amœba divides into two individuals exactly similar to the parent organism and to one another; in short, this little lump is alive.

We find that there is some trace of differentiation even in this primitive organism. Thus towards the centre of the lump is a spherical or oval body (a nucleus), differing slightly in its chemical characters from the surrounding substance, which latter may also be differentiated into an inner granular or spongy portion, the *endosarc*, and a peripheral hyaline material, the *ectosarc*.

The stuff composing the body of the amœba and endowed with vital properties is called *protoplasm*.

The term 'protoplasm' has been used in two senses. By histologists it is confined to a substance found in living bodies, or bodies that were once alive, and reacting in certain ways with certain stains and reagents. In this book however, we shall use the term as a convenient expression for the substance forming the active living basis of all our tissues, although analysis may show considerable differences in its chemical composition in various organs. Protoplasm is in fact living stuff.

The little mass of protoplasm enclosing a nucleus is called a *cell*. Since however there are living organisms in which no trace of a nucleus is to be discovered by the most improved methods, we do not regard its presence as essential to our conception of a cell.

FIG. 1

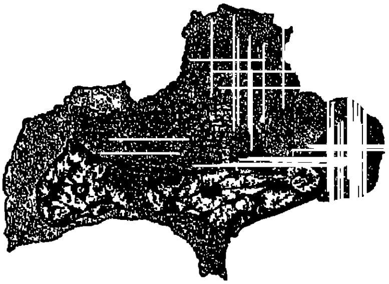


Figure of amœboid corpuscle, highly magnified, showing elongated nucleus, endosarc, and ectosarc (Schafer)

Now we find that all the higher animals, including ourselves, are made up of enormous aggregations of similar nucleated masses of protoplasm, and may be regarded as colonies of amœbæ. But just as in a colony of men, with increasing growth of the community there is increasing differentiation of function, so in us some cells are eminently assimilative and digestive, others respiratory, others motile, while some are set apart for the purposes of reproduction.

Hand in hand with this physiological goes morphological differentiation—that is, the structure of each group of cells becomes modified to fit it for carrying on its own work and its own work alone.

Thus the motor cells do all the external work required by the whole organism, both for purposes of defence and offence. Under this latter head we may class the work of getting food, since this must always be at the expense of some other living organism. In return for this they are supplied with food, water, and oxygen in an assimilable form by the activity of other groups of cells, just as a soldier—the community's instrument of offence and defence—is clothed, fed, and housed at the expense of the community for which he works.

A collection of cells, modified and built up together for some particular function, is called an organ when we are considering its physiological import, or a tissue when we regard only its morphological aspect.

The Assimilation of Food

In some of the lowest forms of animal life, food can be taken in at any part of the surface of the body. In the amœba we can observe the whole process with the microscope, and we see how the particle of food that has been taken in undergoes partial solution—that is to say, part of it disappears and apparently becomes built up into the living stuff of the organism. The remnant that cannot be dissolved is again turned out of the body through any part of the surface.

The processes by which these minute animals assimilate food are very similar to those taking place in man and allied forms, only in the latter we find that there is a differentiation of function, a division of labour in which some cells of the body take up one part of the work of assimilation, while other cells are told off to carry on another part; and we are able to study the whole process much more fully since we can take it bit by bit. In man the work of taking up food is still performed by the surface of the body, but it is a special part of the surface, highly differentiated, and protected by its position and certain mechanisms from coming in contact with anything except food, so that it may devote its whole energies to this one function.

All the higher animals may be considered as built in the form of a tube, the external surface of which is differentiated for purposes of defence, and therefore forms also the organs by which the processes of the body act in harmony with changes in its environment.

The internal surface, on the other hand, is the special alimentary surface, and is called the alimentary canal.

Between these two surfaces the wall of the tube contains the supporting tissues of the body, the bones, etc., and also the organs for the conversion of the potential energy of the food into motion and work, the muscles. In all the highe animals cavities are developed between the two surfaces i the substance of the middle layer—the body-cavities, repre sented in man by the pleural and peritoneal cavities; so tha the alimentary canal for a considerable part of its course i connected with the body-wall only by one side, and seems t hang down into the peritoneal cavity.

The tube of special alimentary cells forming the digestiv canal is surrounded by motor cells derived from the middl layer. These serve to drive the food from one end to th other, and to expel the innutritious matter.

In order to get a greater number of working cells, ther are recesses of the surface lined with cells, which are calle glands, and protuberances in the lumen of the tube, which are called villi. Even among the cells of the alimentary surface there is differentiation of function. Thus the cells of the glands manufacture and pour out fluids, varying in composition and action at different parts, which have the power of moistening and dissolving the constituents of the food, while the cells covering the villi seem more especially adapted for absorbing the food after it has been digested and rendered soluble. The glands may be simple tubular recesses in the mucous membrane, or may branch to such an extent as to form a bulky organ. The liver is a type of such an overgrown process of the alimentary epithelium. This latter organ, however, has other important functions to perform besides the

Fig. 2.

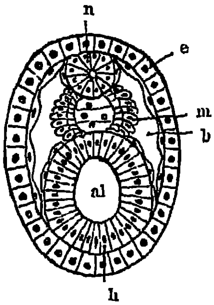


Diagram showing relations of embryonic layers e Epiblastic or outer layer. h. Hypoblastic or alimentary layer m Mesoblastic or middle layer. b Body cavity. n Central nervous system. al Alimentary canal mere solution of foodstuffs. It is to a large extent concerned in further elaborating the foodstuffs after they have been absorbed into the body, so as to make the function of self-nutrition still easier for the other servants of the organism.

We may here run through the various parts of the alimentary canal, with the glands opening into it. From the mouth, where the food is chiefly broken up by the teeth and moistened by the saliva, which is secreted by the *salivary glands*, the food passes through the tubular œsophagus or gullet into the stomach. This is a saccular dilatation of the canal, situated in the upper part of the abdomen. In it the foodstuffs are acted upon by the gastric juice, secreted by small tubular glands, and the dissolved products are partly taken up or absorbed.

FIG. 3.

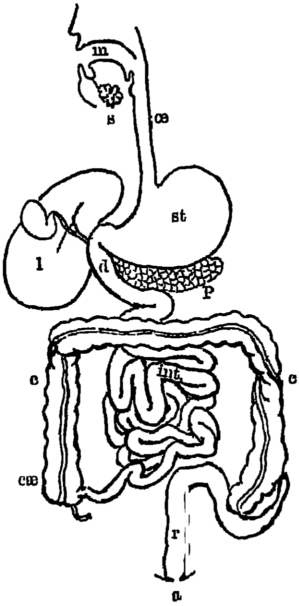


Diagram of alimentary canal m Mouth with salivary glands, s, opening into it œ Œsophagus st Stomach d Duodenum with pancreas, p, and liver, l, opening into it int Small intestine cæ. Cæcum c Colon. r. Rectum a Anus

After the stomach the alimentary canal becomes narrowed again to form the small intestine. In man this is divided into three main divisions—the duodenum, about nine inches long; and the jejunum and ileum, about twenty feet long.

Into the upper part of the duodenum two glands, the liver and pancreas, pour their juices, while the whole internal surface is taken up with villi and tubular glands (crypts of Lieberkühn), so that digestion and absorption go on simultaneously. The ileum leads into the colon or large intestine. This is about twice as wide as the small intestine, from which it is separated by a valve, the ileo-colic valve. Its internal surface is entirely taken up with tubular glands, no villi being present. In this part of the canal absorption probably predominates over digestion. The lower part of the large intestine is the rectum, and opens by an aperture, the anus, on the surface of the body, by which the indigestible residue of the food, forming the fæces, is discharged.

Circulation of the Blood

In order that the foodstuffs taken up by the cells lining the alimentary canal should be distributed to all parts of the body, there must be some means of transporting the food. This means is furnished by the blood. All the tissues of the body are supplied with a close meshwork of delicate tubes, called capillaries, the walls of which are formed by a single layer of cells. This layer is permeable to fluids, so that the surrounding tissues are practically in contact with the blood in the capillary tubes, and can take up nourishment from or give off their effete material to it. These capillaries communicate with larger tubes which have thicker walls, and these lead to and from a hollow organ with thick muscular walls—the heart.

The heart is divided into four cavities, two auricles and two ventricles, each auricle being separated from the adjoining ventricle by valves. These valves are so arranged that, when the heart contracts and diminishes its capacity, the blood can flow only in one direction. We may compare it to an enema syringe in which the compressing force is in the elastic wall instead of being supplied by the hand of the experimenter.

The tubes taking the blood from the heart to the tissues have thick elastic walls, and are called arteries; while those bringing the blood back from the tissues are called veins have thinner and more distensible walls.

Fig. 4.

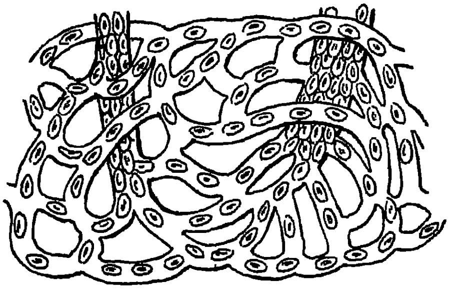


Diagram of capillaries in frog's web

Fig. 5 shows the course taken by the blood in its circulation through the body, as it is impelled by the contracting heart.

Fig 5

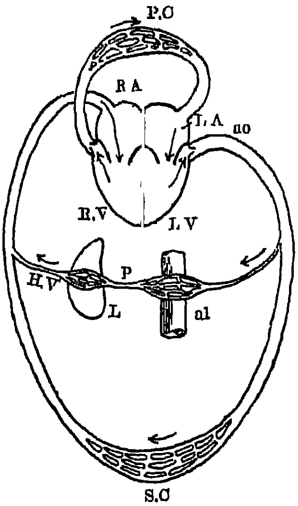


Diagram of circulation L V Left ventricle L A. Left auricle R V. Right ventricle R A Right auricle ao Aorta. S C Systemic capillaries al Alimentary canal P Portal vein L Liver H V Hepatic vein P C Capillaries of lungs

Starting from the left ventricle, the blood is propelled through the aorta into the systemic arteries, and thence into the capillaries supplying the head, neck, body, limbs, and alimentary canal.

From the capillaries of the alimentary canal the blood flows into a number of veins, which unite to form a large vessel, the portal vein. This then enters the substance of the liver and breaks up again into a number of capillaries, which ramify and anastomose round the hepatic cells.

The blood from these capillaries is again collected into a large vessel, the hepatic vein, which flows into the inferior vena cava. This latter vessel also conveys blood from the back, lower limbs, and kidneys.

The superior vena cava with the blood from the upper extremities and head and neck, and the inferior vena cava open into the right auricle.

From the right auricle into the right ventricle, then along the pulmonary artery which breaks up into innumerable capillaries in the lungs (forming the *lesser circulation*), then from the pulmonary capillaries along the pulmonary veins, the blood reaches the left auricle, from which it flows into the left ventricle, having completed its whole circulation.

Respiration and Excretion

We have hitherto spoken of the blood only as a medium for the distribution of food to the various tissues. But it is more than this. Every cell, every protoplasmic unit of the body, to live, must be supplied with oxygen, and must be able to get rid of the products of its activity, namely, CO_2 and urea, or some body allied to urea. In all these functions the blood acts as the middleman between the cell hidden deep in the body and the cell on the surface of the body.

Thus as the blood flows through the lungs, it is separated from the air in the cavities (alveoli) of this organ only by the thinnest possible layer of cells. Here we find that the blood changes its composition, giving up CO_2 and taking in oxygen.

When the blood reaches the tissues, a process the reverse of this takes place ('internal respiration'), the cells of the tissues taking up oxygen and giving up CO_2 to the blood.

The cells also discharge their nitrogenous waste products into the blood, which immediately carries them to the kidneys.

In these organs again we find a single layer of cells between the blood-capillaries and a cavity which is in free communication with the exterior. It is these cells which take up the

FIG 6.

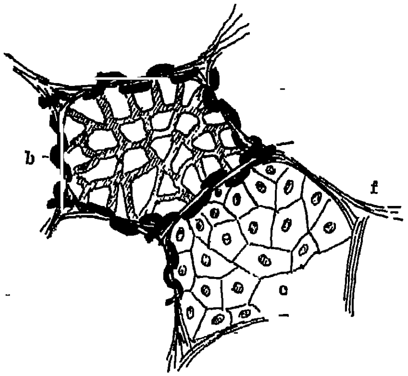


Diagram of lung tissue, showing—b Capillary blood-vessels in walls of alveoli e Epithelium lining the alveoli f. Cut edges of alveolar walls, consisting of connective tissue fibres and elastic tissue

FIG. 7

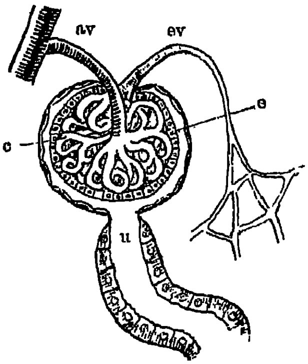


Diagram of kidney av Afferent blood-vessel. ev Efferent blood-vessel. c. Loop of capillaries e Secreting epithelium u Urinary tubule leading to bladder and exterior

waste products of the other tissues from the blood and discharge them into the urinary tubule, together with water and salts, as urine. From the urinary tubule the urine flows down the ureter into the bladder, whence it is voided periodically.

Thus the blood is continually taking up food from the alimentary canal and oxygen from the lungs, and carrying them to the tissues. Here it parts with them and receives in return the products of tissue change (which are indeed only the products formed by the union of the oxygen with the food-stuffs), and carrying these away discharges them on the exterior of the body by means of the lungs and kidneys.

Muscular Tissues

Retaining our comparison of the human body to a heat engine, we have still the most important part of the mechanism to consider—namely, that part in which the heat produced by the oxygenation of the food is converted into motion and so performs work.

This is effected by specialised groups of cells united together to form the muscles. These are fleshy masses attached at two ends to the bones and other supporting tissues of the body. They are capable under certain circumstances of shortening, that is to say, approximating the points to which their two ends are attached against resistance, so that they do work. Thus the biceps muscle of the arm is attached above to the shoulder-blade, and below to the radius, one of the bones of the forearm. When it contracts, it thickens and shortens, and draws up the forearm so as to bend the elbow-joint. Thus it may do work in two ways. If the shoulder is fixed, contraction of the biceps will raise a weight held in the hand; or the hand may be fixed, as in hanging on a horizontal bar, so that the effect of contraction of the muscles is to raise the shoulders and with them the whole body.

We also find muscular tissue, though less highly differentiated, in the interior of the body surrounding the heart, blood-vessels, and alimentary canal. It is by the contraction of these hollow muscular tubes that the blood is set in motion, and the food propelled from one end of the alimentary canal to the other.

Co-ordination and Reaction

Here our analogy of the heat engine must cease. For whereas an engine needs engineers and stokers to determine its work and keep it supplied with fuel, a man's body goes on seeking out food and feeding itself and working for sixty or seventy years.

According as the external circumstances vary, so a man must do more or less work, must take more or less food. Moreover, in such a complicated mechanism as the human body, there must be a delicate adjustment of the actions of the various organs to one another, so that the part which is doing most work should be best supplied with nutriment and oxygen, and no part waste its stored-up energies in doing useless work.

Thus there is an adaptation of the actions of the body as a whole to the requirements of its environment ('necessity'), and also mutual adaptation within the body of the actions of the various organs to one another. This harmonious working of the body and all its parts is effected by the governing and directing power of the central nervous system, the brain and spinal cord of all the higher animals.

In comparing the human body to a tube, we alluded to the outer layer of cells as especially set apart for the purpose of protection, and for regulating the events of the body according to the changes in the environment. Very early in development however, we find that a part of this surface becomes involuted into a groove, the walls of which close over so as to form a canal—the primitive neural canal. The latter then becomes cut off for most of its extent from the external surface by an ingrowth of the middle layer or mesoblast

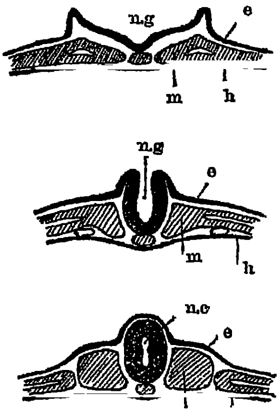
The cells forming the walls of the canal grow and multiply, so that finally the canal is extremely minute in proportion to these walls.

The spinal cord retains this primitive form of a canal with thick walls. At the anterior end of the body (head end) this canal becomes dilated, and sends out lateral and mesial prolongations. The walls of these also become thickened at some places and thinned at others, so that finally a bulky complicated organ is produced which we call the brain.

In figs. 8, 9, and 10 the different parts of the central nervous system are shown diagrammatically, and from these the origin of the whole brain and spinal cord from a simple canal pinched off from the epiblast will be evident.

But this tube of specially 'reactive' or, as we shall always call them, *nerve-cells,* still remains connected with the periphery by strands of protoplasm which we call nerves.

FIG. 8.



Diagrams showing formation of the nervous centre (brain and spinal cord) by a tucking-in of the outer or epiblastic layer. e Epiblast. m Mesoblast h. Hypoblast n c Neural canal. n g. Neural groove.

These strands in many cases end close under the surface of the skin in various forms of cells, specially differentiated for feeling different kinds of stimuli.

FIG 9

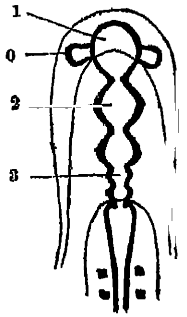


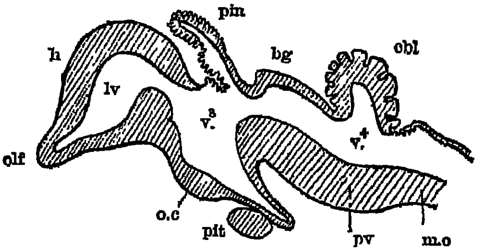
Diagram of the cerebral vesicles of the brain of a chick at the second day (Cadiat) 1, 2, 3 Cerebral vesicles. 0 Optic vesicles

By this means the central system may become aware of all the changes occurring at the periphery of the body.

But it is necessary that the organism should be able to *react* to changes in its surroundings, and we find that very early in the development of the body certain cells in the wall of the tube send out long protoplasmic processes which become connected with the muscles, glands, heart, and blood-vessels. Through these processes impulses descend from the brain or spinal cord in response to stimuli which have proceeded up the sensory nerves from the periphery.

This change in the intra-corporeal events determined change in the extra-corporeal through the intervention o. central nervous system is called a *reflex action*. The mea

FIG. 10.



Longitudinal section through brain of chick of ten days (after Mihalkovicz). olf Olfactory lobes h. Cerebral hemisphere. lv Lateral ventricle. pin Pineal gland. bg Corpora bigemina. cbl Cerebellum o c Optic commissure. pit Pituitary body. pv Pons Varolii m.o Medulla oblongata v^3, v^4. Third and fourth ventricles

of this term must be carefully borne in mind, since we shall meet with examples of it in every stage of our subject. In fact, the whole of an animal's life may be looked upon as one long series of reflex actions.

Perhaps the idea will be rendered more concrete by an example. If we decapitate a frog and then dip one of its toes into dilute acid, the leg is drawn up.

This *reaction* may be prevented in any one of the following ways:

1. Section of the sensory (afferent) nerves from the toes to the spinal cord.
2. Destruction of the spinal cord.
3. Section of the motor (efferent) nerves coming from the cord and running to the muscles.
4. Destruction of the muscles of the leg.

Thus the elements composing a reflex arc are—

(1) A sentient surface (such as the skin) connected by—

(2) A sensory or afferent nerve

(3) To a cell or group of cells, or of nerve-tracts in the central cerebro-spinal axis. This again is connected by—

(4) A motor or efferent nerve to

(5) A muscle or group of muscles.

For muscle in (5) we may substitute gland-cell or any other cell in the body capable of responding by some change in its condition to a stimulus reaching it from the central nervous system.

FIG. 11

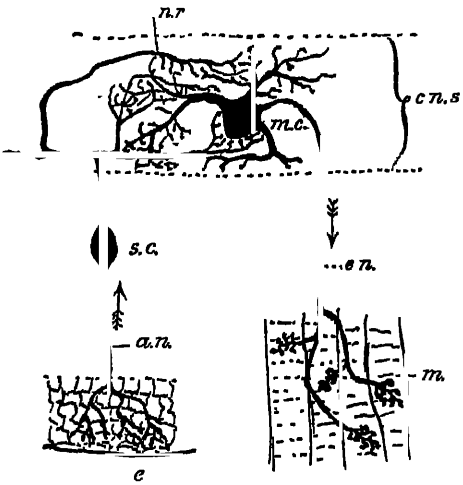


Diagram of reflex action. *e* Sensory epithelium *a n* Afferent nerve-fibre *s c* Sensory cell. *c n s* Central nervous system *n.r.* Branch of sensory cell in close contact with processes of *m c*, motor cell *e n* Efferent nerve-fibre, terminating in end-plates on the muscle, *m*

To fire off a reflex arc, all that is necessary is an appropriate stimulus applied to the sentient surface. Now we find that in all animals almost any form of energy may serve as a stimulus. Thus it may be merely mechanical as when we poke the frog, or chemical, or electrical, or in the form of light, heat, or sound. In every case where a stimulus is applied there is an expenditure of some energy, though the amount may be very slight—a conversion of one of those forms of motion (of masses or molecules) into some other forms of motion which cause or attend the passage of an impulse up the afferent nerve.

It must be noted however that the work done by the stimulus is in no way equivalent to the energy it sets free reflexly. The slightest touch of a pin to the skin causes most powerful reflex movements of the thigh muscles of a decapitated frog. A stimulus in fact acts only by setting free a large amount of potential energy previously stored up in the muscles, which amount may depend on the most diverse circumstances: just as the amount of energy set free in firing a gun depends on the amount of gunpowder in the charge, and not on the size of the fulminating cap used to fire it. This simile however must not be taken too literally. Under normal circumstances a stronger stimulus, within certain limits, will give rise to a stronger evolution of energy (contraction of a muscle, etc.); but in every case the work done by the muscle far transcends in amount the work done in stimulating the muscle.

In all higher animals it is not the whole sensory surface that will respond to all forms of stimuli. Here again there is a division of labour among the sensory cells, some taking on the function of converting light, others heat, others sound, and so on, into a nervous impulse, which may ascend to the central nervous system and there give rise to some form of response as a reflex action.

Thus we have the formation of organs of special sense containing sensory cells, which under normal circumstances react to one form of stimulus, and only one. The eye receives impressions of light, the ear of sounds, special cells in the skin impressions of temperature (heat and cold), and of pressure and touch.

The higher sense-organs, as they are termed—the eye, olfactory organ, and ear—are connected with the upper part of the neural tube, the brain. The end-organs of temperature and touch are distributed over the whole surface of the body, and are connected to the neural tube through its whole length.

The spinal cord has a twofold function. It serves as a conductor of impulses started by stimuli at the surface of the body to the brain, and as a conductor of efferent impulses from the brain. It may also be regarded as a collection of reflex *centres* regulating all kinds of movements and functions.

The nerves, which connect the cord with all parts of the body, are arranged symmetrically on the two sides of the body, so that there are thirty-one pairs of nerves arising from the spinal cord.

Each nerve-trunk at its connection to the cord is divided into an anterior and a posterior root; and we shall show later on that all the impulses leaving the cord pass along the anterior roots, while the posterior roots are composed exclusively of fibres bearing afferent impulses.

A short distance from the cord these two roots join, and the mixed nerve-trunk thus formed divides again and again, supplying the sensory end-organs and muscles of a definite segment of the body.

An important branch of the mixed nerve-trunk (though small anatomically) is the ramus communicans of the sympathetic. The fibres forming this little nerve pass into a chain of ganglia (*i.e.* collections of nerve-cells) situated along the back of the body-cavity, in front of the spinal column, and sending a prolongation up into the neck.

Some of the fibres become connected with these ganglion cells while others simply pass through the ganglion. All the fibres however, before passing to their destination, become connected with nerve-cells situated more peripherally. This destination is all the organs of vegetative life, the alimentary canal, heart, blood-vessels, glands, etc.

The whole system of visceral nerves, formed from the nerve-fibres of the rami communicantes, is called the sympathetic system.

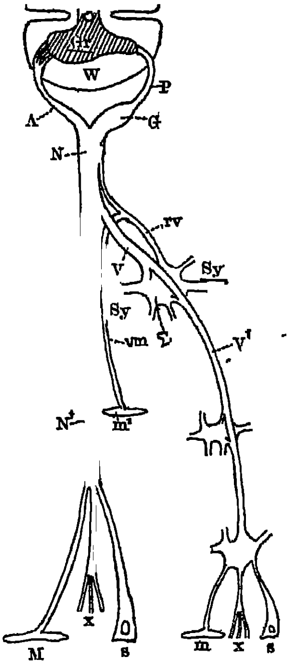
The accompanying diagram will serve to illustrate the general plan of distribution of a single spinal nerve, and its connections with the sympathetic system.

An unending series of reflex actions is going on in our body, and of many of these we may be quite unaware. But in very many cases we learn that something is going on when a stimulus affects our afferent nerves by having what we call a *feeling* or *sensation*. In order to experience a sensation we must be conscious, and therefore sensations are classed with emotions, ideas, volitions, as states of consciousness.

A pure investigation of states of consciousness, however, belongs to the province of the psychologist. We have only to deal with them so far as the function of afferent nerves is concerned, since it is difficult to obtain an objective sign of their activity (though, as we shall see later, such signs are present).

We have evidence that in man and the higher animals consciousness is intimately bound up with the outgrowths from the front of the neural tube, which we call the cerebral hemispheres. On the integrity of these depends also the carrying out of the so-called spontaneous or voluntary move-

FIG. 12.



Scheme of the nerves of a segment of the spinal cord (Foster). Gr. Grey; W, white matter of the cord. A Anterior, P, posterior root G. Ganglion on posterior root N Whole nerve giving off N^1 somatic nerve to muscle M, or sensory cell s, and visceral branch v, which passes through various ganglia of the sympathetic system before reaching the visceral muscle m or sensory cells rv is the grey ramus communicans which runs back from the ganglion Σ to the spinal cord. It gives off a branch vm, which runs in connection with the spinal nerve to the blood-vessels of the limbs Sy The sympathetic chain uniting the ganglia of the series Σ ments—that is to say, movements which are not, so far as we can tell, called forth by any directly preceding stimulus or change in the environment of the animal.

The parts of the brain below the hemispheres seem built up on much the same plan as the spinal cord, and like this contain a collection of reflex centres and nerve-paths. These reflex mechanisms however are very important, since their afferent channels are the important nerves subserving the functions of seeing, hearing, smelling, tasting, etc.

The significance of the cerebral hemispheres in the normal life of the animal can be well shown in the frog. If in this animal we remove the cerebral hemispheres, we find that it still acts in all respects as a normal frog, except that it is incapable of interpreting its sensations or of initiating voluntary acts. If we put it in water, it swims about till it comes to the edge of the basin, when it crawls up and sits on the edge. Stroke its back and it croaks. Put it on a horizontal board, it remains perfectly still. Incline the board, the frog climbs up it. All these complicated movements are brought about immediately by changes in the environment. They are examples of reflex action.

But if we leave the brainless frog to itself, and protected from disturbing influences, it sits there till it becomes a mummy. Having lost the greater part of its consciousness, it can no longer *feel* hungry, it does not *know* its food when it sees it, and therefore does not *will* to move in order to get it.

Reproduction and Heredity

The production of new individuals, the crowning point of an animal's existence, is carried out by means of certain special cells, the spermatozoa in the male and the ova in the female, which represent potentially all the peculiarities of the parent organism. By the union and fusion of parts of a spermatozoon and ovum, a single cell is produced, the fertilised ovum, as it is termed; and from this cell by division and differentiation is formed the new individual, endowed with structures and properties similar to and derived from both parents. The rest of the cells of the body afterwards die, having served their function when they have reared the new family of individuals.

Thus from a broad standpoint all the complicated processes that we study in physiology, all the toil and turmoil of human existence, are nothing but 'the by-play of ovum-bearing organisms.' The biological destiny of man is accomplished with the production and rearing of a new individual.

Now we have shown above that in many respects the body may be regarded as a mechanism, controlled by external circumstances, and converting the potential energy of food into the kinetic energy of warmth and movement.

This comparison is further justified when we find that in all processes of the body there is no creation of energy. All energy possessed by the body is derived from the potential energy contained in the food, which in its turn represents the stored-up energy of the sun's rays.

On these accounts many have thought that no other factors were at work in living bodies than the intermolecular relations which comprise the laws of physics and chemistry, and that even the supreme facts of consciousness might be explained in this manner. But past experience warns us to be very careful before accepting purely physico-chemical conceptions of any vital phenomena. Again and again, as we shall see when discussing the processes of absorption, secretion, respiration, etc., have purely physical explanations been put forward, only to be overthrown by further investigations.

In fact every cell in the body, like a conscious being seems to have a power of selection, a power to eschew the evil and choose the good, the good being that which is necessary to its preservation as a unit of the cell community. A layer of living protoplasm, one twenty-thousandth of an inch in thickness, is able to take up materials on one side and discharge them on the other, in direct opposition to all known physical laws of diffusion and osmosis.

We may discover the functions of a living cell and the conditions of its activity, and, in general terms, the source from which it derives its energy; but beyond this we have been foiled in all attempts to find out how the cell uses the energy of the food for its own aims. It does not at present seem likely that any physico-chemical hypothesis will ever explain how all the physical and intellectual peculiarities may be transmitted from father to son through one single minute cell, a spermatozoön, five hundred millions of which would hardly occupy one cubic millimetre.

We shall therefore in the following pages confine ourselves to a discussion of the functions of the various organs, the conditions of their activity, and the physical and chemical changes which can be demonstrated to occur in the organs concomitantly with their activity.

These objects of physiology are still very imperfectly known, and probably need yet many years of laborious research for their elucidation. But when we are fully acquainted with the laws and conditions of the activities of normal living structures, we shall be able to attack the problems of disease with a sure hope of success; for, knowing how the organism will react to all manner of circumstances, we shall be able to put it into an artificial environment which will counteract the effects of the previous abnormal environment, and so restore the organism to a healthy condition.

CHAPTER II

THE MATERIAL BASIS OF THE BODY

SECTION 1

THE SOURCES OF THE ENERGY OF THE BODY

CAREFUL experiments have shown that there is no creation or destruction of matter in the living organism, that is to say, the principle of the conservation of matter applies within as without the living body. Hence an ultimate analysis of the body reveals the same elements as are found in the earth's crust.

The results of ultimate analysis teach us that twelv chemical elements enter into the composition of all living organisms. These are carbon, hydrogen, oxygen, nitrogen, sulphur, phosphorus, chlorine, potassium, sodium, calcium, magnesium, and iron. They are essential to the life of the animal. Other elements, such as silicon, iodine,[1] fluorine, manganese, are found occasionally, but it is not known whether the minute quantities of these substances which are found are merely accidental or necessary to life.

If the body of an animal be heated with free access of oxygen, the carbon and oxygen are burnt up and escape as carbon dioxide and water; the nitrogen is eliminated as ammonia or in the free state, and the rest of the elements remain as the ash.

One hundred parts of the ash of a young dog contain (Bunge)—

K_2O	8 5
Na_2O	8 2
CaO	35 8
MgO	1 6
Fe_2O_3	0 34
P_2O_5	39 8
Cl	7 3

---

[1] Iodine seems to be an invariable and essential constituent of the active principle of the thyroid gland (*vide* Chap XII)

Most of these constituents of the ash exist in the tissues as salts, either free or in a very loose state of combination with other substances.

Nearly all the iron, sulphur, and a considerable amount of the phosphorus however are found in the body, not as salts, but as complicated organic compounds with proteins and allied bodies.

The same elements are found in plants, although here certain of the non-essential elements may occur in greater quantities than they do in the case of animals. Thus silica forms a large proportion of the ash of certain grasses, although a normal growth can be obtained in the almost entire absence of this substance.

All these elements are derived by plants from the atmosphere or from the earth's crust. Here however the substances, which present themselves as foodstuffs to the plant, are in a state of maximum oxidation, and are devoid of potential energy, the mineral matters occurring as salts, the carbon as the CO_2 of the atmosphere, and the nitrogen as minute traces of ammonia or nitrites. In the plant these elements are built up into substances which can develop energy by combustion, and therefore are possessed of potential energy. This energy is put into the plant by the sun's rays. The green parts of plants are able to utilise the radiant energy of certain parts of the spectrum in the splitting up of CO_2, giving off the oxygen to the atmosphere, and building up the carbon into complex compounds, of which the earliest appear to be sugar and starch. It is supposed that the first change which occurs is a formation of formaldehyde, $CO_2 + H_2O = CH_2O + O_2$, and that this formaldehyde by simple condensation yields a carbohydrate of the formula $C_6H_{12}O_6$. The plant thus obtains a store of potential energy, which it can utilise for the formation of still higher products or for the synthesis of such bodies as fats and proteins. All three classes of substances, proteins, fats, and carbohydrates, are built up together with salts and water to form the unstable material which, as the chemical basis of life, is known as protoplasm.

In animals this power of utilising the sun's rays for the synthesis of complex organic substances from CO_2 and nitrites or ammonia is wanting. They are therefore dependent for their life on the co-existence of plants. On these they feed, taking in their food in the form of proteins, fats, and carbohydrates. In the animal body these substances are oxidised, setting free once more the energy which had been snatched by the plant from the sun's rays, and are excreted in their original form as CO_2, and ammonia or allied bodies such as urea.

A marked distinction thus seems to obtain between the chemical processes in plants and animals. In the former the processes are chiefly synthetic, while in the latter they are chiefly oxidative. No hard and fast line however exists between the two classes of living beings. The power of splitting up CO_2 is confined to the chlorophyll granules of plants. In all other parts of plants, and perhaps in these granules themselves, a process of respiration is also going on, in which oxygen is absorbed and CO_2 is given off; and in the entire absence of oxygen every plant, except certain anaerobic bacteria, dies. Respiration therefore is a common function of all protoplasm, and is merely hidden in green plants exposed to sunlight by the more energetic assimilative function of the chlorophyll granules.

Although the animal body cannot build up proteins, fats, and carbohydrates from ammonia and CO_2, yet, given these three classes of foodstuffs, it can from these carry out many complicated synthetic processes. Thus it was long ago shown by Wohler that benzoic acid administered to an animal was excreted in the urine as hippuric acid. In this case a synthesis of benzoic acid with glycine (amino-acetic acid) had taken place.

$$C_6H_5.COOH + CH_2NH_2COOH = C_6H_5.CO\ CHNH_2COOH + H_2O.$$

We shall have occasion to discuss many other examples of synthetic processes occurring in the animal body. The best known are perhaps the formation of fats from carbohydrates, and the formation of the complex conjugated proteins, nucleo-proteins, etc., from the simple proteins, fats, and carbohydrates of the food.

Although therefore we must allow to all protoplasm, whether vegetable or animal, synthetic as well as disintegrative powers, the fact remains that the one source of the energy of the animal body is the disintegration and oxidation of the compounds presented to it in its food. Now all substances can be divided into two classes: those which undergo spontaneous combination with oxygen, such as phosphorus or an alkaline solution of pyrogallic acid, which may be termed auto-oxidisable, and those which are unaffected at ordinary temperatures by oxygen, which may be termed dysoxidisable. To the latter class belong the foodstuffs, and the question arises, by what means their oxidation is effected in the living body. Outside the body we can effect a combination of these substances with oxygen by raising their temperature to a red heat, but this method is obviously inapplicable within the body. The difficulty is that, at ordinary temperatures, molecular oxygen, O_2, is relatively inert, the combining affinities of each of its atoms being satisfied within the molecule, $O=O$. Oxidation however can at once be effected if by any means we can break up this molecular compound, so as to leave the combining affinities of the two compounds unsaturated. Many theories have been put forward as to the manner in which this *activation* of the oxygen is carried out in the body. Thus it has been suggested that the total oxidation occurs, so to speak, in two stages. By the ordinary disintegrative processes, reducing (auto-oxidisable) substances are formed, and these combining with oxygen split up the oxygen molecule, leaving one half of the molecule free to attack less readily oxidisable substances. Many such instances are known of the simultaneous progression of reducing with oxidative processes. Thus ozone is formed in the slow oxidation of phosphorus by the air. The oxidation of pyrogallol in ammoniacal solution is associated with the conversion of a certain amount of the ammonia into ammonium nitrite. Of the existence of reducing substances in the body we have ample evidence. Thus methylene blue injected into the living animal undergoes reduction in the tissues, forming a colourless compound which is re-oxidised to methylene blue on exposure to the atmosphere. It is difficult however to decide whether these reducing substances are formed as by-products in the cell metabolism, or whether they are an integral part of the protoplasmic molecule, as was imagined by Pfluger.

Closely allied to this process is the oxidation which is associated with the splitting up of a molecule of water. Thus if benzaldehyde is shaken up with water and air, it becomes oxidised to benzoic acid, and at the same time can effect oxidation of other dysoxidisable substances. In this case a water molecule is split up into H and OH, the OH group taking the place of the H in the aldehyde group (COH) of the benzaldehyde, while the two hydrogen atoms set free combine with an atom of oxygen to form water, thus releasing an atom of oxygen in the active state and therefore ready to effect other oxidations.

According to other authorities, the mechanism of oxidation in the body is similar to that employed in the manufacture of sulphuric acid. In this case sulphur is burnt to form SO_2, and then nitric oxide, NO, is added together with air. The NO combines with the oxygen of the air to form NO_2, and this reacts with the sulphurous acid to form SO_3 and NO. The NO thus acts as a carrier of oxygen between the air and the SO_2. In the same way an ammoniacal solution of cupric hydrate, which is reduced on boiling with dextrose, becomes at once blue again on exposure to the air, and can be used to oxidise an indefinitely large quantity of the dextrose. In these cases we can make precise chemical equations for the various steps of the oxidation. In other cases this is not possible. Thus spongy platinum will effect a rapid union of hydrogen and oxygen to form water. Here there is no evidence of the formation of an oxide of platinum as an intermediate stage of the process, and we say that the substance acts katalytically. In all cases however it is difficult to explain why the presence of a third substance should render the oxidation possible. We have here an example of a whole series of phenomena in chemistry, where the presence of a factor, which adds nothing to the total energy of the reaction, yet materially alters the velocity of the reaction, often rendering a reaction possible which without it would take an infinity of time for its accomplishment.

It has been definitely shown that substances can be extracted from the blood and tissues of animals and from the substance of plants, which possess the property of effecting certain oxidations, and have therefore been termed oxygen carriers or oxygen ferments (*oxydases*). The exact chemical character of these substances is undetermined, though in some cases they seem to belong to the class of nucleo-albumens.

It is of course possible that all these methods are made use of in the living cell for the oxidation of foodstuffs. It is certain that the oxidation is not accomplished at one stroke, but that it proceeds by stages. It will be our office later on to try to trace out some of these stages, and so obtain some idea of the history of the foodstuffs in the body.

2616 L:3 N07

IISc Lib B'lore

SECTION 2

THE PROTEINS

Since our chief foods are derived from other living organisms, a consideration of the proximate constituents of our bodies covers that of the proximate constituents of the food. These can be divided into three main classes, proteins which contain nitrogen and sulphur, fats, and carbohydrates. Of these the proteins are the most important, since they represent the only irreplaceable portions of the food. Many animals can live on a pure diet of proteins, and even in man fats and carbohydrates are largely interchangeable; but in no case can the place of proteins be taken by any other substances.

Proteins are found in all protoplasm, and are more abundant in those tissues where growth is actively going on. They are, in the condition in which we generally come across them, amorphous, indiffusible, and varying in their solubilities. They are inert bodies, tasteless, and presenting no distinct acid or basic characters. Although it is possible to obtain certain proteins in a crystalline condition, they all belong to the class of bodies known as colloids.

The term 'colloid' was applied by Graham to distinguish certain substances such as egg-albumen or gum or gelatin, from easily crystallisable substances such as salts and sugars Whereas the latter are easily diffusible through animal membranes, colloids are absolutely indiffusible All colloids appear to possess very large molecules, and it is possible that their indiffusibility is connected with this fact It is difficult however to be certain that the apparent solutions of colloids in water are really strictly comparable with such a solution as that of sodium chloride In many cases the apparent solution is really only a suspension of fine particles, and very simple means will suffice to bring most colloidal solutions into such a condition of suspension. All colloidal solutions may, under favourable conditions, present the phenomenon of coagulation, a phenomenon which depends on an alteration of the relations between suspended particle and solvent, and on an aggregation of the smaller into larger particles, which may fuse to form networks This coagulated condition may be brought about by various means by the application of heat, by simple mechanical shaking, or in some cases by the mere addition of neutral salts In some cases the reaction is reversible Thus gelatin and water form a solid jelly when cold, but become fluid when the temperature is raised An alkaline solution of casein, to which calcium chloride has been added, forms a solid clot when warmed, but becomes fluid again at a normal temperature, and a similar phenomenon is observed in the early stages of the action of pancreatic juice on milk In most cases however the action is irreversible Silicic acid, which has been coagulated by the addition of neutral salt, cannot be dissolved again on removing the salt by dialysis. The coagulum which is formed in a solution of egg albumen by heating is permanent, and insoluble in weak acids or alkalies or in salt solutions A colloidal membrane permits as a rule the free passage of water and salts, but is impermeable for dissolved colloids, so that on filtering a colloidal solution under pressure through a colloidal membrane, the filtrate consists simply of water with salts, all the colloid remaining behind on the filter

All proteins contain oxygen, hydrogen, nitrogen, carbon, and sulphur, and their compositions vary round the following numbers.

C . . .	50·6 —54·5 per cent
H . . .	. 6·5 — 7·3 „
N . . .	. 15·0 —17·6 „
S . . .	. 0·3 — 2·2 „
P .	0·42— 0·85 „
O .	21·50—23·50 „

Of the sulphur a certain portion is oxidised, while the rest exists in the unoxidised condition, and can be split off as a sulphide by boiling with caustic potash or soda. Hence we must assume the presence of at least two atoms of sulphur in the protein molecule, and this assumption enables us to arrive at the smallest possible empirical formulæ of many proteins. Some of these formulæ may be given here, since they serve to indicate the enormous size and complexity of the molecules of this class of substances.

Egg albumen .	$C_{204}H_{322}N_{52}O_{66}S_2$.
Protein in hæmoglobin (from horse) .	$C_{680}H_{1098}N_{210}O_{241}S_4$.
„ „ (from dog) .	$C_{725}H_{1171}N_{194}O_{214}S_2$
Crystallised globulin (from pumpkin-seeds)	$C_{292}H_{181}N_{90}O_{83}S_2$.

Crystallisation of proteins —It has long been known that proteins occur in the crystalline form in the seeds of certain plants, as in hemp-seeds, paranut, and pumpkin and castor-oil seeds These crystals, which are known as aleuron grains, consist of proteins belonging to the class of globulins By mechanical means they can be separated from the surrounding tissues, and after washing dissolved in a solution of magnesia On dialysing this solution against alcohol, the fluid is gradually concentrated, and crystalline granules of the magnesia compound of the protein separate out These crystals contain 1·4 per cent MgO, pointing to a molecular weight of the protein of about 2800 (If X be the molecular weight, $\frac{X}{40} = \frac{100-1·4}{1·4}$, therefore X = 2817)

It is also easy to crystallise egg albumen and serum albumen. White of egg is treated with an equal bulk of saturated solution of ammonium sulphate to precipitate the globulins, and filtered The filtrate is rendered slightly acid with dilute acetic acid, which is added until a slight precipitate is formed The mixture is put aside for twenty-four hours, at the end of which time the greater portion of the albumen has been precipitated as fine needle-shaped crystals These may be freed from ammonium sulphate by washing with a saturated acidified solution of sodium chloride A similar method is used in the case of serum-albumen By repeated crystallisation a product may be obtained which is absolutely constant in both its physical and chemical characters. (Hopkins)

THE STRUCTURE OF THE PROTEIN MOLECULE

We can only arrive at some idea of the manner in which the protein molecule is built up, by breaking it down bit by bit, employing methods which will not act too forcibly in changing the whole arrangement of the constituent parts of the molecule. In the body almost all the protein is converted into urea or carbamide $\left(\mathrm{CO}<^{\mathrm{NH_2}}_{\mathrm{NH_2}}\right)$, in which form it is excreted, but we have evidence that the urea is formed by a synthetic process from ammonium carbonate or carbamate, which must therefore be regarded as the last stage in the physiological disintegration of protein. In the body many substances are found which are presumed to be intermediate stages in the conversion of protein into urea. Owing however to the coincidence of synthetic with disintegrative changes in the body, it is impossible to assign these substances their exact place in the protein metabolism until we have thrown more light on protein disintegration by chemical experiments. In order to study this question therefore we split up the protein molecule by simple hydrolysis. For this purpose we may heat the protein in sealed tubes with baryta water, or treat it with very active hydrolytic ferments, such as the trypsin of the pancreatic juice. The most convenient method however is to heat the protein for twenty-four hours with a mixture of hydrochloric acid and stannous chloride. (The use of the latter is to prevent any coincident oxidative changes, which would tend to destroy the primary products of hydrolysis.)

We obtain in this way an acid fluid containing an extremely complex mixture of various substances, which may be regarded as the proximate constituents of the protein molecule. They may be classified as follows:—

(a) *Mon-amino-acids of fatty series.*

Glycine (amino-acetic acid)
Alanine (amino-propionic acid)
Serine
Leucine (amino-caproic acid)
Aspartic acid ([illegible]
Glutamic acid

(b) *Mon-amino-acids of aromatic series*

Tyrosine (oxyphenyl-alanin)
Phenyl-alanine
Tryptophane
Proline (pyrrolidine-carboxylic acid)

(c) *Di-amino acids.*

- Ornithine (di-amino-valerianic acid)
- Lysine (di-amino-caproic acid)

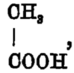
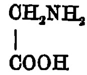
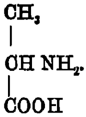
(d) *Bases* Hexone :. containing 6 at

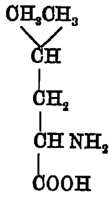
Ammonia
Arginine
Histidine

(e) *Sulphur-containing body*

Cystine

The amino- or amido-acids are derived from the fatty acids by the replacement of one atom of hydrogen in the radicle by the group amidogen, NH_2.

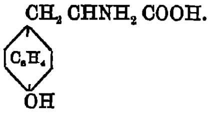
Thus from acetic acid  $\begin{array}{l} CH_3 \\ | \\ COOH \end{array}$, we get amino-acetic acid or glycine  $\begin{array}{l} CH_2NH_2 \\ | \\ COOH \end{array}$; from propionic acid, amino-propionic acid or alanine  $\begin{array}{l} CH_3 \\ | \\ CH\,NH_2 \\ | \\ COOH \end{array}$. *Leucine* is amino-caproic acid, and has the formula



Aspartic acid is amino-succinic acid, $C_2H_3(NH_2)(COOH)_2$, and *glutamic acid* is the next higher homologue in the same series, $C_3H_5(NH_2)(COOH)_2$.

In all these bodies, the acid characters of the group COOH are almost neutralised by the presence of the basic group NH_2, so that the amino-acids as a whole are inert substances with very feeble acid qualities. They can indeed act as bases, giving crystalline compounds with the mineral acids.

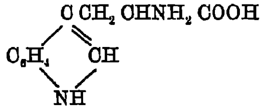
Tyrosine is the chief aromatic amino-acid which occurs in acid protein digests. It is formed by the combination of a fatty amino-acid with an aromatic group, being para-oxyphenyl-amino-propionic acid



Both leucine and tyrosine may be prepared by evaporating down a solution of proteins which have been acted on for twenty-four hours with pancreatic juice. When the liquid is allowed to cool, crystals of tyrosine separate out. These crystals form slender needles arranged in sheaves or radiating from a centre. The mother-liquor is evaporated to a syrupy consistence, extracted with alcohol, and the extract allowed to stand. As the alcohol evaporates, yellowish-brown spheres, consisting of masses of ill-formed needle-shaped crystals of leucine, separate out.

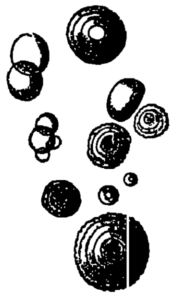
A solution of tyrosine with Millon's reagent gives a red colour, the tint of which deepens on heating.

When proteins are hydrolysed by means of trypsine, the proteolytic ferment of pancreatic juice, the digest at a certain period gives a rose colour on acidification and addition of bromine water. This reaction is due to the presence of another aromatic body, called *tryptophane,* which is a derivative of indol, being indol amino-propionic acid.



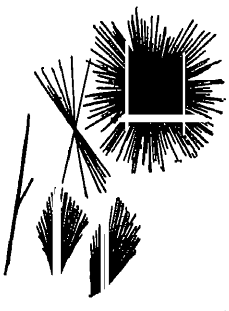
Acted on by bacteria of putrefaction this body gives rise to indol and skatol, substances with a pronounced fæcal odour and constantly produced in the putrefaction of proteins.

FIG 13



Leucine 'cones' (imperfect crystals) (Frey)

FIG. 14

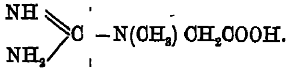


Tyrosine crystals (Frey)

After separating all the monamino-acids, a considerable amount of the original protein remains unaccounted for. Of this remainder a certain amount is present in the form of the *hexone bases,* so called from the fact that they all contain six atoms of carbon in their molecules. These bases can be thrown down from the mother-liquor after the separation of the amino-acids, or from the original acid decoction by the addition of phosphotungstic acid. Three of these bases have been isolated—lysine, arginine, and histidine.

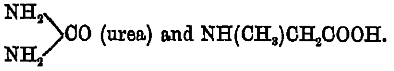
Lysine has the formula $C_6H_{14}N_2O_2$, and is a diamino-caproic acid, the insertion of another NH_2 group into leucine conferring on this body strongly basic properties.

Arginine ($C_6H_{14}N_4O_2$) was first prepared from the seedlings of certain plants. Its chief interest lies in the fact that on boiling with baryta water, it is split up, giving as one of its decomposition-products urea. We thus see that a certain proportion (not more than one-ninth) of the urea which is excreted by the body may be derived by a process of simple disintegration of the proteins of the food, without any accompanying oxidation. Arginine belongs to the same class of bodies as creatine—an important constituent of all muscular tissues. Creatine or methyl-guanidin-acetic acid has the formula



$$\left.\begin{matrix}NH\\NH_2\end{matrix}\right\rangle C\ \vdots\ -N(CH_3)\,CH_2COOH.$$

On boiling creatine with baryta water, it takes up a molecule of water and splits into two halves in the situation of the dotted line in the formula, giving



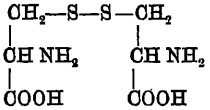
$$\left.\begin{matrix}NH_2\\NH_2\end{matrix}\right\rangle CO\ \text{(urea) and}\ NH(CH_3)CH_2COOH.$$

This latter substance is known as sarcosine, and is derived from glycine by the replacement of one atom of hydrogen by a methyl group, CH_3.

Arginine has a similar formula. On the left-hand side of the dotted line the formula would be identical with that of creatine. On the right-hand side however, the sarcosine group is replaced by a diamino-acid of the fatty series, diamino-valerianic acid or ornithin.

Histidine has the formula $C_6H_9N_3O_2$. It contains the alanine group, being imidazol amino-propionic acid. It does not yield urea on boiling with baryta water.

Nearly the whole of the sulphur in the protein molecule exists or can be separated in the form of cystine. This substance is a crystalline solid, which under some conditions may occur in considerable quantities in the urine (cystinuria), and in such cases may give rise to a urinary calculus. It can be regarded as a sulphur derivative of lactic acid $CH_3.CHOH.COOH$, or of amino-propionic acid $CH_3.CHNH_2.COOH$, and has the formula



$$\begin{array}{ccc} CH_2\text{—}S\text{—}S\text{—}CH_2 \\ \begin{array}{cc} | & | \\ CH\,NH_2 & CH\,NH_2 \\ | & | \\ COOH & COOH \end{array} \end{array}$$

Other amino-acids and allied substances, besides those mentioned, occur in various tissues and fluids of the body. Since however they do not lie on the direct line of protein katabolism, we shall consider their chemical properties in connection with the organs in which they occur.

A comparison of the relative amounts of these substances to be obtained by the decomposition of different proteins shows marked variations, pointing to fundamental differences in their constitution. This is well seen in the following table, in which is given the relative proportions of the more important decomposition products —

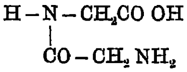
—	Casein (of milk)	Globin (from hæmoglobin)	Edestin (a vegetable protein from hemp-seeds)
Glycine	0	0	3·8
Alanine	0·9	4·2	3·6
Leucine	10·5	29·0	20·9
Glutamic acid	10·7	1·7	6·3
Aspartic acid	1·2	4·4	4·5
Tyrosine	4·5	1·3	2·1
Phenylalanine	3·2	4·2	2·4
Proline	3·1	2·3	1·7
Lysine	5·8	4·2	2·0
Arginine	4·8	5·4	11·7
Histidine	2·6	10·9	1·0
Cystine	0·06	0·3	0·25
Tryptophane	1·5	present	present

A class of bodies known as protamines occurs in the heads of spermatozoa of salmon and some other fishes in combination with nucleic acid. The protamines react in many ways like proteins, giving the biuret reaction. When they are hydrolysed by strong hydrochloric acid, they give off nearly all their nitrogen in the form of the 'hexone bases,' arginine, lysine, and histidine. They give also small amounts of monamino-acids. It has been suggested by Kossel that the typical protein molecule may be regarded as a nucleus composed from the hexone bases, to which is tacked on a number of monamino-acid groups, the relative proportion of the bases in the nucleus, as well as of the subsidiary amino-acids, differing according to the nature of the protein in question. According to this view, the protamines would represent the simplest type of protein.

Most nuclei, including the spermatozoa of most animals, contain another class of bodies, called *histones*, in combination with the nucleic acid. Histones give the ordinary protein reactions, their chief characteristic being the fact that they are precipitated by ammonia. Their disintegration products are such as would be obtained from a mixture or combination of ordinary protein with a protamine Thus, roughly speaking, on hydrolysis by means of acids, the ordinary proteins of our food and tissues give about 10 per cent. of hexone bases, histones about 20 to 25 per cent, while protamines yield about 90 per cent of lysine, arginine, and histidine.

Polypeptides —E. Fischer has succeeded in uniting two or more molecules of various amino-acids to form large molecules which give the biuret reaction, and might be regarded as elementary proteins or parts of proteins. Some of these bodies may be hydrolysed by trypsine (the proteolytic ferment of pancreatic juice) into their constituent amino-acids. To these synthesised substances Fischer has given the name polypeptide. Examples of such bodies are glycyl-glycine, leucyl-tyrosine, glycyl-leucyl-tyrosine.

A similar body—namely, glycyl-alanine—has been obtained directly by the hydrolysis of silk, which suggests that these combinations actually occur as part of the constituent framework of proteins. As a type of the manner in which these substances are built up, we may give the formula of glycyl-glycine:—



$$\begin{array}{l} H-N-CH_2CO\,OH \\ \quad\;\; | \\ \quad\;\; CO-CH_2\,NH_2 \end{array}$$

General Tests for Proteins

1. On boiling proteins in a very slightly acid solution, they are coagulated, and form an insoluble white precipitate.

The best method of carrying out this test is to boil the solution in neutral or slightly alkaline solution, and then while in active ebullition to drop in dilute (1 or 2 per cent) acetic acid until the reaction is slightly acid If the solution is poor in salts, 1 or 2 per cent of NaCl should be added at the commencement. By this means a nearly perfect separation of all the coagulable proteins may be effected

2. On pouring a solution of protein carefully down the side of a test-tube containing strong nitric acid, so as to form a layer on the top, a white layer of coagulated protein is produced at the junction of the two fluids.

3. Acetic acid and potassium ferrocyanide give a white precipitate.

4. Saturation of protein solutions with ammonium sulphate causes complete precipitation of all proteins present.

5. All coagulable proteins are completely precipitated by adding to their solutions an equal bulk of 10 per cent. trichloracetic acid, or of a 5 per cent. solution of metaphosphoric or of salicyl-sulphonic acid.

6. All proteins are precipitated and coagulated by the addition of solutions of picric acid, mercuric chloride, copper sulphate, tannic acid, or of strong alcohol.

7. Excess of caustic potash or soda with a drop of dilute copper sulphate gives a violet colour (Piotrowski's reaction). 1

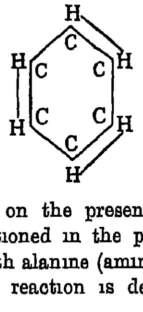
8. On adding strong nitric acid to a protein solution and boiling, a yellow colour is produced which turns to deep orange when ammonia is added (xanthoproteic reaction). 2

9. Millon's reaction. An acid solution of nitrate of mercury gives a white precipitate which turns a brick-red on boiling. 3

10. On adding some weak glyoxylic acid (prepared by the action of sodium amalgam on oxalic acid) to a protein solution and then some strong sulphuric acid, a deep red-purple coloration is produced (Adamkiewicz-Hopkins reaction). 4.

Meaning of the Protein Tests—The last four of these tests are of interest as throwing some light on the constituent parts of the protein molecule. 1 Thus Piotrowski's reaction (often called the biuret reaction) depends on the presence in the protein molecule of groups having the formula $\begin{array}{l}CH_2-NH_2\\ \vert\\ CO-NH\end{array}$, and is given by a number of substances in which two $CO\,NH_2$ or $CH_2\,NH_2$ groups are coupled together either directly, or by a NH or CH_2 group Since the terminal NH_2 group is destroyed by nitrous acid, this acid at once destroys the power of proteins to give the biuret reaction

2 The xanthoproteic reaction depends on the presence in the protein molecule of an aromatic group with the benzene-nucleus.—



3 Millon's reaction depends on the presence of a hydroxy-derivative of benzene, and is mainly conditioned in the protein by the tyrosine group, a compound of hydroxyphenyl with alanine (amino-propionic acid)

4 The Hopkins-Adamkiewicz reaction is determined by the tryptophane group in the protein molecule

CLASSIFICATION OF PROTEINS

The only satisfactory classification of proteins would be one founded on an exact study of their disintegration products. Since however we do not know all these products in the case of even a single protein, it is obviously impossible to attempt any classification on such a basis, and we have therefore to make use temporarily of a purely artificial classification based on the solubilities of the various proteins in water and salt solutions. The fact that simple mechanical shaking may convert a globulin into a coagulated protein will serve to illustrate how entirely artificial is our present mode of classification. Adopting the solubilities as a basis, we may divide the proteins into the following classes:

1. **Native Albumens.**—These are soluble in pure water and are precipitated by saturation with sodio-magnesium sulphate or with ammonium sulphate.

✓ *Egg albumen* forms the greater part of the white of egg. [illegible] It gives the ordinary protein tests, and is precipitated if H_2SO_4 shaken up with a drop of dilute sulphuric acid and excess of ether. It rotates the plane of polarised light to the left 35·5°. If injected into the circulation it gives rise to albuminuria and is partially excreted by the kidneys.[1]

✓ *Serum albumen* occurs in large quantities in the blood- not if plasma and serum, and in small quantities in most tissues of H_2SO_4 the body. It coagulates at 75° C., and is distinguished from egg albumen by its greater specific rotatory power (56°), and by the fact that it is not precipitated by ether and sulphuric acid, and if injected into the circulation does not reappear in the urine.

2. **Globulins.**—These bodies are insoluble in pure water and require a certain amount of neutral salt present to dissolve them. They are the most interesting of all protein groups, playing an important part in nearly all vital processes.

---

[1] This statement has given rise to the idea that the cells of the kidney are permeable to egg albumen but not to serum albumen. This idea is not warranted The fact is that egg albumen is, or contains an ingredient which is, poisonous and injures the kidney cells These therefore become permeable to proteins, and albuminuria results But the proteins of the urine are those which normally occur in albuminuria, viz serum albumen and serum globulin, containing however a certain amount of the foreign protein circulating in the blood, namely egg albumen.

But it must be remembered that we are not justified in speaking of the globulins which we extract from the tissues and treat by precipitation and washing till they are no longer altered by these processes, as the active agents in the complex protein interactions which make up the sum of vital phenomena. Our purified protein is a wreck, and represents merely the framework on which the living protoplasmic molecule was built up.

All the globulins are precipitated from their solutions by saturation with magnesium sulphate and partially by saturation with sodium chloride. The chief members of this class are—

1. *Crystallin*, obtained from the crystalline lens by passing a stream of CO_2 through an aqueous extract of this body.
2. *Paraglobulin.*
3. *Fibrinogen.*
4. *Myosin* or *paramyosinogen.*

These three bodies will be considered in the chapters on blood and muscle.

3. Derived Albumens.—These may be regarded as compounds of proteins with acids or alkalies.

Acid albumen is formed by the action of warm dilute acids or by strong acids in the cold on any of the preceding bodies. If an alkaline solution be added so as to nearly neutralise the solution of acid albumen, this latter is precipitated. If the precipitate be suspended in water and heated, it is coagulated and becomes insoluble in dilute acids or alkalies.

Alkali albumen is formed by the action of strong caustic potash on white of egg or on any other protein, or by adding alkali in excess to a solution of acid albumen. It is precipitated on neutralisation of its solution.

In close association with this group may be included the proteins as they occur in combination with the metallic salts, such as copper sulphate. On splitting off the copper moiety from these compounds, the protein left is practically free from ash, and behaves in many respects like an albuminate, being insoluble in absolutely pure water, but easily dissolved by the addition of a trace of free acid or alkali.

An interesting group of protein derivatives has been described by Hopkins, produced by the action of the free halogens on protein solutions. We get in this way two definite classes of compounds. One class, which contains the largest percentage of halogens, is obtained by treating a protein solution with chlorine, bromine, or iodine, dissolving up the resultant precipitate in alcohol and pouring the alcoholic solution into ether, when the halogen compound is thrown down as a fine white precipitate By dissolving up this precipitate in weak soda and precipitating with acid, we obtain a series of compounds containing only about one-third as much of the halogen as is contained in the first precipitate, suggesting that the halogen forms both substitution and additive compounds with the protein molecule.

4. Fibrins.—The chief of these is blood-fibrin, a stringy protein formed in the clotting of the blood and giving solidity to the clot. It is insoluble in water and salt solutions. In dilute hydrochloric acid it swells up, and if kept at 40° C. it dissolves with the formation of acid albumen. If suspended in water and heated it is coagulated, and is no longer capable of swelling up in dilute hydrochloric acid. Similar bodies, myosin- and myogen-fibrin, are formed in the coagulation or rigor of voluntary muscle.

5. Coagulated Proteins.—Any member of the preceding classes, when heated in a neutral or slightly acid solution, is converted into coagulated protein. In this condition it is insoluble in water, saline solutions, or weak acids. It is dissolved by strong acids or alkalies or by the digestive ferments such as the gastric and pancreatic juices.

HYDRATED PROTEINS

When proteins are subjected to the action of superheated water or steam, or are heated with acids, or acted on at the body temperature by certain ferments (trypsine or papain), they undergo a change which is supposed to be attended with the addition of one or more molecules of water to the protein molecule (hydrolysis). The final result of this action is the group of nitrogenous bodies, chiefly belonging to the amino-acids, which we have already dealt with. As intermediate products in this series of hydrolytic changes, we find a group of bodies, still presenting many of the protein reactions, which are classed as hydrated proteins, and include the proteoses or albumoses and the peptones.

1. Albumoses.—These are all precipitated from their solutions by saturation with ammonium sulphate. On addition of nitric acid they give a precipitate in the cold, which is dissolved on heating but reappears on cooling. On adding an excess of caustic potash and a drop of *very dilute* copper sulphate to a solution of albumoses, a pink colour is produced (biuret reaction). If more copper sulphate be added, the pink colour is changed to violet similar to that produced in a solution of proteins.

According to their solubilities three varieties of albumoses may be distinguished:

a. Proto-albumoses.—Soluble in pure water; precipitated by saturation with sodium chloride or ammonium sulphate. With acetic acid and potassium ferrocyanide it gives a white precipitate.

b. Hetero-albumose.—Insoluble in pure water; soluble in weak saline solutions or dilute acids; precipitated by saturation with salt, or by acetic acid and potassium ferrocyanide.

c. Deutero-albumoses.—Soluble in pure water; not precipitated by saturation with common salt, except after addition of a little strong acetic acid; entirely precipitated by saturation with ammonium sulphate. They give no precipitate with acetic acid and potassium ferrocyanide.

2. **Peptones.**—Soluble in pure water; diffusible through animal membranes; with caustic potash and copper sulphate they give the same reaction as albumoses. From the latter class peptones are distinguished by the fact that they are not precipitated at all by saturation with ammonium sulphate or with any neutral salt.

Albumoses and peptones give the xanthoproteic and Millon's reactions common to all proteins; and like these are precipitated by tannic acid, mercuric chloride, and potassio-mercuric iodide.

CONJUGATED PROTEINS

This name may be applied to various complicated bodies, which resemble one another only in the fact that in each of them a protein radical is combined with some other body.

1. **Hæmoglobin,** the red colouring matter of the blood, is readily crystallisable. On boiling an aqueous solution it splits up into coagulated protein (globin) and an iron-containing body named hæmatin ($C_{32}H_{32}N_4O_4Fe$). Its properties will be described in the chapters on blood and respiration.

2. **Nucleo-proteins.**—These are a group of bodies occurring in large quantities in the protoplasm of cells. They are also found in the chyle, in lymph, and in blood-plasma. They consist of protein combined with a nitrogenous body

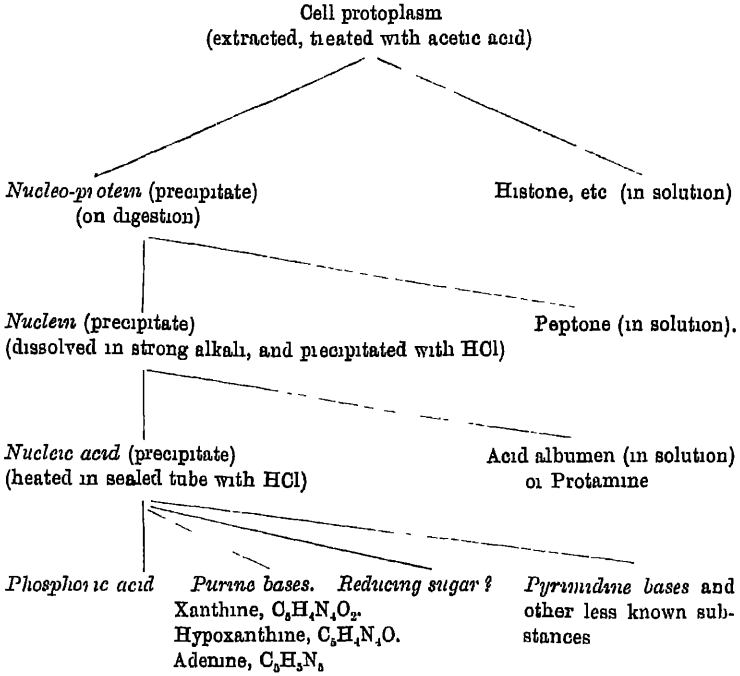
rich in phosphorus called nuclein. As they occur in the cells, they are in most cases soluble in water or in salt solutions, but after separation they need the presence of free alkali for their solution. When subjected to gastric digestion, they are split up, the protein half being converted into albumoses and peptones, while the nuclein is precipitated. The nuclein thus obtained is a white amorphous powder, insoluble in water, salt solutions, or acids, but soluble in strong alkalies. It forms the chief constituent of cell nuclei, and consists of a combination of protein, or protamine, or histone, with a complex body containing nitrogen and phosphorus known as nucleic acid.

When the latter is heated with strong acids, it breaks up into phosphoric acid and a number of other substances, amongst which the most important are bases allied to uric acid and belonging to the xanthin or purin series (xanthin, hypoxanthin, adenin).

In many cases a carbohydrate is found among the products of disintegration of nuclein. As first extracted from the animal cell, the nucleo-proteins are associated with a considerable proportion of lecithin, and in this fresh labile condition form the tissue-fibrinogens of Wooldridge. To prepare these substances, an organ rich in cells such as the thymus is minced and extracted with water or normal salt solution. After separating the cells by means of the centrifugal machine, the clear fluid is decanted off and acidified with acetic acid. A precipitate is produced, consisting of tissue-fibrinogen. This substance is soluble in excess of acid and is easily soluble in alkalies. All the tissue-fibrinogens are highly unstable bodies and undergo changes in the mere act of precipitation and resolution. When injected into the blood, they cause intravascular clotting. On digestion with gastric juice, they yield a precipitate of nuclein, and this precipitate contains a large proportion of the lecithin present in the original substance.

These complex bodies form the greater part of the protoplasm of a living cell. The chromatic part of the nuclei appears to be formed in most cases of nuclein, but the purest nuclear material at our disposal, the heads of spermatozoa, is found to consist almost entirely of a definite compound of nucleic acid and either protamines or histones, so that the essential chemical constituents of a living cell are here reduced to their simplest possible expression.

The chemical relationships of the nucleo-proteins may be rendered clearer by the following table.


Cell protoplasm
(extracted, treated with acetic acid)
Nucleo-protein (precipitate)
(on digestion)
Histone, etc (in solution)
Nuclein (precipitate)
(dissolved in strong alkali, and precipitated with HCl)
Peptone (in solution).
Nucleic acid (precipitate)
(heated in sealed tube with HCl)
Acid albumen (in solution)
or Protamine
Phosphoric acid
Purine bases.
Xanthine, $C_5H_4N_4O_2$.
Hypoxanthine, $C_5H_4N_4O$.
Adenine, $C_5H_5N_5$
Reducing sugar?
Pyrimidine bases and other less known substances

The caseinogen of milk is often grouped with the nucleo-proteins, since like them it gives a phosphorus-containing precipitate on digestion with gastric juice. Like them too it is precipitated by the addition of excess of acid and is soluble in alkalies. The precipitate however which is yielded by gastric digestion is not a true nuclein, since it does not give the xanthin or purin bases on heating with hydrochloric acid. It seems in fact to be little more than an insoluble compound of phosphoric acid with protein, and has been termed pseudo-nuclein or paranuclein. The precipitate is stated to be absent in the case of caseinogen of human milk. With rennet ferment caseinogen undergoes coagulation, forming casein or cheese (*v*. Chap. VIII.). Caseinogen, with certain other proteins presenting similar properties, are often put in a distinct class as the phospho-proteins.

3 **Glyco-proteins.**—This class of bodies is of considerable interest, since in many cases its members may represent stages in the upbuilding of carbohydrates in the protoplasmic molecule. They have been regarded as glucosides of the proteins, but in all cases where the carbohydrate moiety has been isolated in a state approaching purity, it has been found to contain nitrogen. Probably therefore in most instances the conjugation is not between glucose and protein, but between a body of the composition of glucosamine and protein.

Glucosamine was first procured by boiling the chitinous shells of crustacea with hydrochloric acid. It is formed from a molecule of grape-sugar or other hexose by the replacement of an OH group by NH_2. In chitin this substance occurs in combination with acetic acid or some derivative of acetic acid. A somewhat similar substance is found in the cartilage of vertebrates. The cartilage matrix contains two chief substances, chondro-mucoid and chondrin. By long extraction with weak alkali, a paired acid, *chondroitin-sulphuric acid*, can be extracted from both these bodies, leaving behind in the case of chondro-mucoid a substance of the protein class, in the case of chondrin pure gelatin. On boiling the chondroitin-sulphuric acid with weak acid it is decomposed, with the formation of a body, *chondrosin*, which reduces Fehling's solution and appears to be compounded of two derivatives of glucose, viz. glycuronic acid ($C_6H_{10}O_7$) and glucosamine ($C_6H_{11}O_5.NH_2$).

It is possible that many so-called simple proteins contain a small amount of a carbohydrate residue wrapped up in their molecule. Thus from egg albumen, even crystallised, it is easy to prepare a reducing substance which gives a definite osazone. We have seen moreover that a carbohydrate may occur in the decomposition of nucleic acid. In the typical glyco-proteins however, the carbohydrate moiety forms a much greater part of the molecule than in the last two cases. They may be classified as follows.

1. *Mucins*. Mucin occurs in the saliva, and as a product of secretion of the mucous glands throughout the alimentary tract, and as a skin-secretion in many lower animals. It also forms an important constituent of the ground substance of connective tissue, from which it may be extracted by treat-

ment with lime or baryta water. On boiling with dilute mineral acids, it is converted into an acid-albumen and a reducing substance containing nitrogen which appears to be isomeric with glucosamine, and has been called *mucosamine.* Owing to its content of protein it of course gives the ordinary protein tests. It swells up in water, forming a viscid slimy mass. It is precipitated by acetic acid, and is insoluble in excess of this reagent. It is soluble in dilute alkalies.

2. *The mucoids* include a number of substances, such as *colloid, ovo-mucoid, pseudo-mucin,* which are obtained from ovarian cysts and other pathological formations. They also appear to be glucoside-like combinations of a protein with some body allied to glucosamine, or the anhydride of such a body.

3. *The chondro-proteins* include substances which are compounded of chondroitin-sulphuric acid and protein. One example of this class we have already mentioned under the name of *chondro-mucoid.* Another important substance is the *amyloid substance* or *lardacein* which is found in the middle coats of the blood-vessels, in the liver, and other organs under certain pathological conditions. It is insoluble in water, alkalies, acids, or gastric juice. It gives a red-brown colour with iodine, which, on the addition of strong sulphuric acid, turns to a dirty-blue colour.

BODIES ALLIED TO PROTEINS, OR ALBUMINOIDS

Under this heading we may group a number of diverse bodies.

1. *Gelatin* may be extracted from all connective tissues, especially bone and white fibrous tissue, by prolonged boiling with water. It forms a solution in water, which is liquid at high temperatures but sets into a jelly when cold. It is precipitated by tannic acid, but not by acetic acid. No tyrosine can be formed from it by boiling with dilute sulphuric acid, and on this account pure gelatin does not give a red colour when boiled with Millon's reagent. Gelatin is not present as such in the tissues, but is formed from a precursor (*collagen*) by prolonged boiling with water.

2. *Chondrin* may be extracted by boiling cartilage Its solutions are precipitated by acetic acid, and form a jelly when cold. On boiling with dilute acids it is split up, with

the formation of a body possessing the power of reducing Fehling's solution. It has been shown that chondrin is a compound of gelatin with a sulpho-acid (chondroitin-sulphuric acid, *q.v.*, p. 45).

3. *Elastin*, the substance of which the yellow fibres of connective tissue are composed, is insoluble in water and dilute acids or alkalies. It is very slowly dissolved by gastric juice.

4. *Keratin* forms the main part of the horny layer of the skin, nails, hair, hoofs, etc. It is very insoluble. It presents the same elementary composition as the proteins, but is distinguished from them by the very large quantity of sulphur present, which may amount to 5 per cent. A very similar substance, *neuro-keratin*, can be obtained from the supporting framework (neuroglia) of nervous tissues.

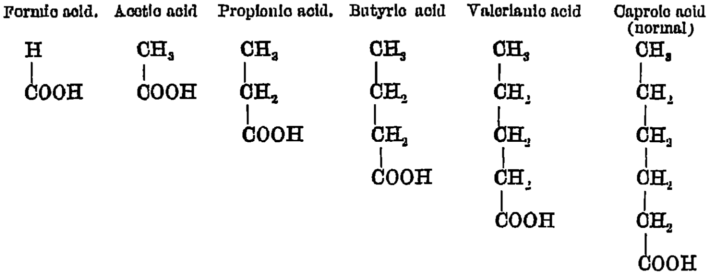
Both elastin and keratin give the colour-reactions of proteins, especially the xanthoproteic and Millon's reactions.

SECTION 3

THE FATS

These bodies consist of the elements carbon, hydrogen, and oxygen. They occur to some extent in most tissues and form the greater part of adipose tissue.

The lower acids of the fatty series are represented by formic, acetic, propionic, butyric acid, etc., and have the general formula $C_nH_{2n}O_2$. The following formulæ will serve to show the manner in which they are built up.



$$\begin{array}{cccccc}
\text{Formic acid.} & \text{Acetic acid} & \text{Propionic acid.} & \text{Butyric acid} & \text{Valerianic acid} & \text{Caproic acid (normal)} \\
H & CH_3 & CH_3 & CH_3 & CH_3 & CH_3 \\
| & | & | & | & | & | \\
COOH & COOH & CH_2 & CH_2 & CH_2 & CH_2 \\
 & & | & | & | & | \\
 & & COOH & CH_2 & CH_2 & CH_2 \\
 & & & | & | & | \\
 & & & COOH & CH_2 & CH_2 \\
 & & & & | & | \\
 & & & & COOH & CH_2 \\
 & & & & & | \\
 & & & & & COOH
\end{array}$$

Thus by adding the group CH_2 a whole series of bodies can be formed increasing in molecular weight. The 16-carbon acid is palmitic acid, and the 18-carbon acid is known as stearic acid.

Besides these we have another group of the general formula $C_nH_{2n-2}O_2$, in which two of the CH_2 groups are replaced by two CH groups linked by double bonds, thus $\begin{matrix}CH\\ \|\\ CH\end{matrix}$. To this group belongs the other chief acid of the fats, viz. oleic acid, $C_{18}H_{34}O_2$.

The fat of adipose tissue consists of a mixture of olein, palmitin, and stearin, the first being liquid and the two latter solid at ordinary temperatures.

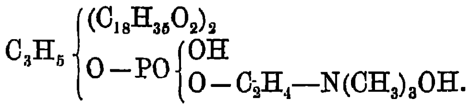
Fats may be considered as compounds of the triatomic alcohol, glycerin ($C_3H_5(OH)_3$), with oleic, stearic, or palmitic acid, water being eliminated in the act of combination. Thus:

$$\underset{\text{Glycerin.}}{C_3H_5(OH)_3} + 3\underset{\text{Oleic acid}}{(C_{18}H_{33}O.OH)} = \underset{\text{Olein.}}{C_3H_5(O.C_{18}H_{33}O)_3} + \underset{\text{Water.}}{3H_2O}.$$

Fats are insoluble in water, but soluble in ether and in hot alcohol. When boiled with alkaline solutions, they are split up with the formation of glycerin and a compound of the fatty acid with the alkali, which is called a *soap*. The alkaline soaps are soluble in water.

In the fats of milk (butter) we find lower acids of the fatty series, such as *butyric*, *caprylic*, and *caproic* acids, combined with glycerin. *Acetic acid* is also a member of the fatty acid series. It occurs in the body as an amino-acid, *glycine*.

Lecithin.—This substance is a wax-like body which is universally distributed in the organism, and is found in especially large quantities in the white matter of nerves and of the spinal cord. It may be regarded as a compound of a molecule of glycerin with two of stearic acid, one of phosphoric acid, and a molecule of a nitrogenous base, cholin. Its composition is represented by the following formula :

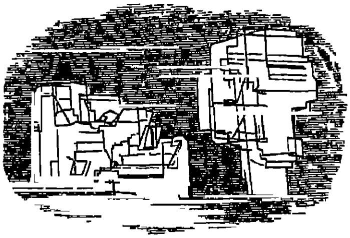


$$\mathrm{C_3H_5}\begin{cases}\mathrm{(C_{18}H_{35}O_2)_2}\\ \mathrm{O-PO}\begin{cases}\mathrm{OH}\\ \mathrm{O-C_2H_4—N(CH_3)_3OH.}\end{cases}\end{cases}$$

Lecithin is miscible in all proportions in ether, alcohol, and fats. It swells up in water, of which it can imbibe a large quantity.

Cholesterin may be considered here although it does not belong to the group of fats. Like lecithin it is found wherever protoplasm is present and seems to be an essential constituent of every living cell. It is a monatomic alcohol ($\mathrm{C_{26}H_{43}.OH}$). It is easily soluble in ether or hot alcohol. From the latter it is deposited on cooling in typical plate-like

FIG 15.



Cholesterin crystals

crystals, each of which has a corner knocked out. It is insoluble in water but slightly soluble in a solution of bile-salts. Its history and use in the body are absolutely unknown.

Tests for cholesterin.—(1) On dissolving cholesterin in chloroform and then adding an equal volume of concentrated sulphuric acid, the cholesterin solution becomes first blood-red and then a more violet-red, while the sulphuric acid appears dark red with green fluorescence

(2) On moistening cholesterin crystals with sulphuric acid diluted with one-fifth of its bulk of water, the edges of the crystals become reddish and then violet. If a little iodine solution be now added, the crystals become by degrees violet bluish-green, and then blue.

SECTION 4

THE CARBOHYDRATES

These substances occur in large quantities in plants, and therefore are important constituents of the food. Only small amounts of carbohydrates however are at any given time present in the body, where they may occur as sugar or animal starch, or built up with proteins and allied bodies into more complex compounds. They all consist of carbon, hydrogen, and oxygen, both the latter substances being present in the same proportions as they exist in water. Their general formula is therefore $C_mH_{2n}O_n$. They may be divided into three classes: mono-saccharides, di-saccharides, and poly-saccharides.

1. The Mono-saccharides

These bodies are all ketone or aldehyde derivatives of polyatomic alcohols. Thus from alcohols of the formula $C_6H_{14}O_6$ may be derived by oxidation either the aldehyde, d-glucose or grape-sugar, $CH_2OH(CHOH)_4COH$, or the ketone, d-fructose or lævulose, $CH_2OH(CHOH)_3CO.CH_2OH$.

The sugars (of which grape-sugar is a type) containing the aldehyde group —COH, are spoken of as *aldoses*. Those which, like lævulose, contain the ketone group—CO—are called *ketoses*.

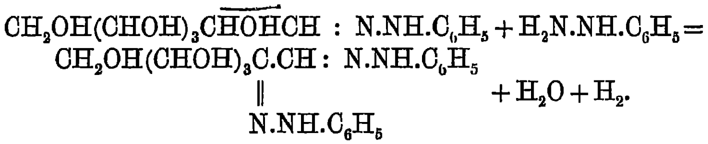
The di- and poly-saccharides are derived from the mono-saccharides by a process of condensation attended with the elimination of water. The mono- as well as the di-saccharides are all distinguished by names ending in —ose. Thus according to the number of carbon atoms present, we may distinguish trioses, tetroses, pentoses, hexoses, etc. Of the sugars only those with six carbon atoms, viz. the hexoses, which are of physiological importance, need concern us here.

All the sugars resemble the ordinary aldehydes in being possessed of strongly reducing properties. Thus they reduce cupric to cuprous hydrate on boiling, and ammoniacal solutions of silver to the metallic condition. From a practical standpoint one of their most important reactions is that with phenylhydrazine. On boiling an aqueous solution of sugar with phenylhydrazine and acetic acid, two sets of bodies are formed, first *hydrazones* and then *osazones*. The reaction which goes on is represented by the following equations:

$$\underset{\text{Glucose}}{CH_2OH(CHOH)_3CHOH.CHO} + \underset{\text{Phenylhydrazine}}{H_2N.NH.C_6H_5} =$$

$$\underset{\text{Phenylglucosehydrazone}}{CH_2OH(CHOH)_3CHOH.CH : N.NH.C_6H_5} + H_2O.$$

The hydrazone then reacts with another molecule of phenylhydrazine to produce an osazone.



$$\begin{array}{l} CH_2OH(CHOH)_3C\overline{HOH}CH : N.NH.C_6H_5 + H_2N.NH.C_6H_5 = \\ \quad \begin{array}{l} CH_2OH(CHOH)_3C.CH : N.NH.C_6H_5 \\ \qquad\qquad\qquad\quad \| \\ \qquad\qquad\quad N.NH.C_6H_5 \end{array} + H_2O + H_2. \end{array}$$

The hydrogen however is not given off in the free state but acts on a third molecule of phenylhydrazine, splitting it into aniline ($C_6H_5 NH_2$) and ammonia.

The osazones are yellow crystalline compounds, which have definite solubilities and melting-points, varying according to the sugars from which they have been derived. Hence these compounds are of great value in the separation and identification of sugars in a complex mixture. By acting on the osazones with reducing agents, such as zinc and acetic acid, an osamine is formed, *e.g.* glucosamine, and from this a sugar can be re-obtained by the action of nitrous acid In this case however the sugar is always a ketose, so that we may in this way convert glucose into fructose or lævulose.

A very large number of hexoses are known, the differences depending partly on the variations in the structural formulæ, partly on the varying position of the constituent atoms of the molecule. Owing to the asymmetric structure of the molecules, there are three sugars corresponding to each structural formula. Two of these are optically active and rotate the plane of polarised light either to the right or to the left, while a third modification is inactive and can be regarded as consisting of an equal number of molecules of the two active varieties. It is customary to classify the glucoses into d- (dextro-rotatory), l- (lævorotatory), and i- (inactive) groups, and to distinguish the other sugars by the letters of the glucose with which they are most nearly connected, without any reference to their optical characters. Thus fructose or lævulose, although it is lævo-rotatory, is distinguished as d-fructose owing to its relationships with grape-sugar, d-glucose.

The different varieties of sugars are however easily convertible one into the other. Thus by the action of weak alkalies, glucose is converted into fructose and mannose and two other sugars.

A number of the mono-saccharides are acted upon by yeast with the formation of alcohol, CO_2 being evolved in the process. This action however is confined to the mono-saccharides with three, six, or nine carbon atoms. Moreover certain of the artificially prepared hexoses, as well as some occurring in combination with proteins in the glyco-proteins, are insusceptible to the action of yeast.

Of the numerous hexoses known, we need only describe three which are of physiological importance, *i.e.* grape-sugar, galactose, and fructose or lævulose, the two first being aldoses while the latter is a ketose.

Grape-sugar (d-glucose) or dextrose is found in small quantities in the blood and in numerous tissues of the body, and is the form to which all carbohydrates are converted before they reach the circulation. It occurs in large quantities in grapes and, mixed with lævulose, in honey and various fruits. When pure it forms colourless crystals which are easily soluble in water. Its solutions rotate the plane of polarised light to the right.

Tests for dextrose.—1. Moore's test. On warming a solution of dextrose with caustic potash or soda, the solution turns first yellow and then brown.

2. Trommer's test. On adding caustic potash or soda to a solution of dextrose and then a few drops of copper sulphate, the cupric hydrate produced is dissolved to form a deep-blue fluid solution. On heating to boiling, the cupric is reduced to cuprous hydrate, which is thrown down as a yellow or red precipitate. Fehling's reaction is merely a modification of this test. An alkaline solution of cupric hydrate is prepared by adding Rochelle salt and potash to a solution of copper sulphate, the tartrate serving to keep

the cupric hydrate in solution. On boiling some of this 'Fehling's solution' with dextrose, it is reduced with the production of the red cuprous hydrate. The proportions of the ingredients are so adjusted that 1 c.c. of Fehling's solution is exactly reduced by 0·005 gramme dextrose.

3. The phenylhydrazine test for sugar has already been described. The phenylglucosazone forms masses of yellow needle-shaped crystals which, when purified by recrystallisation from alcohol, melt at 204° C.

Lævulose, fruit-sugar or d-fructose, occurs in fruits and honey in association with dextrose. It is also produced by the hydrolysis of a species of starch called inulin, and together with dextrose by the inversion of cane-sugar. It gives the same tests as dextrose, but rotates the plane of polarised light to the left.

Galactose is obtained together with dextrose by the inversion of milk-sugar, and is also present in the glucoside, cerebrin, which is found in the brain. It rotates the plane of polarised light to the right.

2. The Di-saccharides

The di-saccharides can be regarded as anhydrides formed by the combination of two mono-saccharides with the elimination of one molecule of water. Hence their general formula is $C_{12}H_{22}O_{11}$. Under the action of hydrolytic agents they take up a molecule of water and split into two molecules of hexose. Thus

Cane-sugar + H_2O = dextrose + lævulose.
Lactose + H_2O = dextrose + galactose.
Maltose + H_2O = dextrose + dextrose.

Cane-sugar is the most important member of this group, and takes a prominent place in our dietary. It is crystalline and easily soluble in water. On boiling with dilute mineral acids or under the action of certain ferments, it undergoes inversion, taking up one molecule of water and splitting into dextrose and lævulose.

$$\underset{\text{Cane-sugar.}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Dextrose.}}{C_6H_{12}O_6} + \underset{\text{Lævulose.}}{C_6H_{12}O_6}.$$

Under the action of the yeast fungus, cane-sugar is first inverted, and the invert-sugar is then converted into alcohol with the ebullition of CO_2.

$$\underset{}{C_6H_{12}O_6} = \underset{\text{Alcohol}}{2C_2H_6O} + 2CO_2.$$

Cane-sugar does not reduce alkaline solutions of cupric hydrate such as Fehling's solution. When warmed with sulphuric acid it turns black. On adding concentrated hydrochloric acid to a strong solution of cane-sugar and heating, the fluid turns a deep-red colour. The same reaction is given by lævulose, but not by dextrose.

Lactose or *milk-sugar* occurs in milk. It is much less soluble in water than cane-sugar and is only faintly sweet. It reduces Fehling's solution. On boiling with dilute acids it takes up water and is converted into dextrose and the isomeric sugar known as galactose.

$$\underset{\text{Lactose.}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Galactose}}{C_6H_{12}O_6} + \underset{\text{Dextrose}}{C_6H_{12}O_6}.$$

With the lactic acid organism it is converted into lactic acid. To this conversion of lactose into lactic acid is due the souring of milk.

$$\underset{\text{Lactose}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Lactic acid}}{4C_3H_6O_3}.$$

Maltose is the end-product of the action of diastase, salivary or pancreatic ferments on starch. It reduces Fehling's solution and is converted on boiling with dilute mineral acids into dextrose.

3. The Poly-saccharides

This group includes a large number of highly complex bodies which all occur in the amorphous condition and belong to the class of colloids. Their general formula is $(C_6H_{10}O_5)x$, where x may be anything from twenty up to a hundred or more. By hydrolysis they are all converted finally into mono-saccharides. They may be divided into three groups, starches, dextrins and gums, and celluloses; but we need concern ourselves here only with those members which are of physiological importance.

Starch does not occur in the living body, but constitutes an important foodstuff, being present in large quantities in nearly all vegetable food. It is a white powder consisting of microscopic grains with concentric rings. It is insoluble in cold water. When boiled with water, it swells up to form an opalescent semi-solution. This solution gives an intense blue colour with iodine. On boiling with dilute acids, starch is converted first into dextrin and then into dextrose. With various ferments, such as diastase (malt ferment), salivary or pancreatic ferments, it undergoes hydrolysis and is converted into dextrin and maltose. The change that occurs on boiling with acids may be thus represented:

$$\underset{\text{Starch.}}{C_6H_{10}O_5} + \underset{\text{Water.}}{H_2O} = \underset{\text{Dextrose.}}{C_6H_{12}O_6}.$$

Glycogen or animal starch is found in the liver, muscles, and other tissues of the body, and occurs in especially large quantities in all fœtal tissues. It is a white powder soluble in cold water, forming an opalescent solution. With iodine it gives a mahogany-red colour. It is affected by acids and ferments in the same way as starch. It is precipitated from its solution on the addition of alcohol to 60 per cent. It is moreover precipitated by saturation of its solutions with ammonium sulphate.

Dextrin. Two varieties of this body may be distinguished according to their reaction with iodine—*erythrodextrin* which gives a red colour with iodine; and *achroodextrin* which gives no colour.

It is said to occur in small quantities in blood, muscle, and liver, but it is chiefly of importance as being an intermediate product in the digestion of starch. It is gummy and amorphous, readily soluble in water but insoluble in alcohol and ether. On boiling with acids it is converted into dextrose. It is not thrown down on saturation with ammonium sulphate.

Cellulose is the colourless material which composes the cell-walls and woody fibre of plants, and so occurs to a large extent in our food. In man however it does not undergo digestion and therefore need not be further considered here.

In herbivorous animals cellulose undergoes digestive changes, and forms an important constituent of their food In this case the digestion is mainly effected through the intermediation of micro-organisms, and results in the formation of acetic and butyric acids and marsh gas, besides other substances In certain invertebrata a true cellulose-digesting ferment (*cytase*) is secreted by the walls of the alimentary canal

CHAPTER III

THE BLOOD

SECTION 1

THE FORMED ELEMENTS OF THE BLOOD

THE blood, which circulates through all parts of the living body and comes into close relationship with all the tissues, acts as a medium of communication between the cells in the interior of the body and those on the surface. Thus it carries the absorbed foodstuffs, which have been taken up by the cells lining the alimentary canal, to all the other cells of the body, and from these receives in exchange their waste products, CO_2 and urea, or some precursor of these substances, to discharge them through the intermediation of excretory cells on the surface or lining involutions of the outer surface of the body, such as the cells of the skin, kidney, and lungs.

It is evident that the composition of the blood must be always varying, according to the nature of the tissues it has just traversed, and these variations will be more fitly considered when we come to the discussion of the activities of the various tissues. But we find that the blood has a certain power of regulating its composition, or perhaps this function [illegible] ascribed to the various tissues through which the [illegible]. However this may be, the fact remains that the blood has an average composition which it is our duty in this chapter to describe, and round which its composition varies only to a certain (definite) extent.

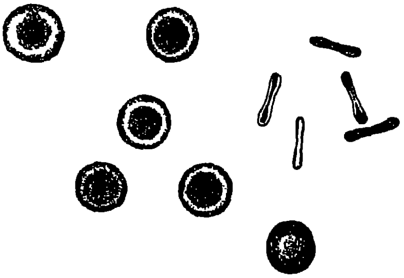
The blood of man and most vertebrates is a red opaque liquid, rather viscous, and to the naked eye homogeneous. Arterial blood, *i.e.* the blood in the pulmonary veins, left side of the heart, and the arteries generally, is bright scarlet; while venous blood, *i.e.* blood in the systemic veins, right heart, and pulmonary artery, is of a bluish-red hue.

Shaking up venous blood with air or oxygen changes it to arterial blood, and we shall see later that the bright colour is due to the formation of a loose combination of one of the constituents of the blood, hæmoglobin, with oxygen. This combination is normally formed in the lungs, and is robbed of its oxygen in the tissues.

On microscopic examination the blood is found to consist of a nearly colourless fluid, the *liquor sanguinis* or *blood-plasma*, holding in suspension an enormous number of solid bodies, the *red* and *white blood-corpuscles.*

The colour of the blood is entirely due to the red corpuscles. These are, in man, non-nucleated biconcave discs about $\frac{1}{3200}$ of an inch in diameter, and a third of this in thickness. The colour of a single corpuscle is yellow, the red colour being apparent only when large numbers of them are seen together. They form about 40 per cent. of the total mass of the blood, there being about five million red corpuscles in every cubic millimetre of blood.

FIG. 16.



Non-nucleated red blood-discs of human blood On the right of the figure the corpuscles are seen on edge. (Swale Vincent)

They are soft, flexible, and elastic, so that they can readily squeeze through apertures and canals narrower than themselves without being permanently distorted. Each red corpuscle consists of a framework or *stroma* composed chiefly of protein material, containing in its meshes or in a state of loose chemical combination with it, a red colouring matter, hæmoglobin, to which is due the colour of the corpuscles and of the blood itself.

By treating the blood with weak solutions of tannic or boracic acid, a separation occurs between the hæmoglobin and the stroma. The hæmoglobin appears as a small ball near the centre of a colourless blood-disc, or it may be extruded and lie just outside the stroma. If the plasma be made denser by evaporation or by addition of salts to it, water diffuses from the corpuscle into the plasma, and the corpuscle shrinks and becomes wrinkled or *crenated*. If on the other hand the plasma be diluted, water diffuses from the surrounding medium into the corpuscle, which swells up and becomes spherical.

It is found that in a 0·9 per cent. solution of sodium chloride the red corpuscle of mammalian blood neither gains nor loses in volume. In solutions of less concentration the corpuscle swells, while in those of greater concentration the corpuscle shrinks and becomes crenated. These facts show that the external limiting layer of the corpuscle is impermeable to sodium chloride, but permits the easy passage of water to equalise the concentration within and without the corpuscle.

This movement of water is due to the fact that dissolved substances, like gases, are always tending to expand within their solvents, a tendency which gives rise to *diffusion* from places of higher to those of lower concentration, or to a pressure (*osmotic pressure*) on any membrane or wall which is permeated by the solvent but which prevents the passage of the dissolved substances. When the corpuscles are immersed in a weak salt solution, the osmotic pressure within the corpuscle is greater than that outside, so that the corpuscle expands, and may indeed burst if the difference of concentration is sufficiently great. In solutions of higher concentration, the external osmotic pressure is greater than that in the corpuscle, and water is squeezed out through the limiting layer, so that the corpuscle shrinks.

It is evident that these changes of form will occur only when the corpuscles are immersed in a solution of some substances which cannot penetrate the corpuscle. Most neutral salts (*e.g.* $NaCl$, Na_2SO_4, KNO_3 &c.) belong to this category. A solution of urea, on the other hand, behaves towards the corpuscles like distilled water. If some red corpuscles be added to a 1 per cent. solution of urea in normal saline solution (0·9 per cent. $NaCl$), they neither shrink nor swell; and if the mixture be centrifuged, and the corpuscles and supernatant fluid analysed separately, the percentage of urea in the two cases will be found identical—though there will be a great preponderance of sodium chloride in the supernatant fluid. There are a large number of substances besides water to which the corpuscles are permeable (and in this respect they resemble most other vegetable and animal cells), *e.g.* alcohol, chloroform, ether, etc. Speaking generally, we may say that animal cells are freely permeable to all those substances which are soluble in fats and the allied *lipoid* substances, cholesterin, lecithin, and protagon, which are invariable constituents of all living cells. If, for instance, we wish to stain a living cell, we must choose some dye-stuff which is soluble in this class of bodies.

In birds, amphibia, and fishes, the red corpuscles differ from those of mammals in being nucleated Those of the frog for instance are oval structures, each containing an oval nucleus with a well-marked nuclear network The hæmoglobin is diffused through the protoplasm of the cell-body, and does not extend to the nucleus Mammals during the early part of their fœtal life also possess nucleated red corpuscles These however soon disappear entirely, to make way for the ordinary non-nucleated red discs In the camel the red corpuscles are oval in shape like those of the frog, but possess no nucleus They are also much smaller than those of the frog

The colourless corpuscles, or *leucocytes*, are rather larger than the red ($\frac{1}{2500}$ inch in diameter), and much fewer in number, there being only one white corpuscle to about 800 to 600 red.

They are colourless nucleated masses of protoplasm very similar to the simple organism described in the Introduction as the amœba. Like this they have the power of moving from place to place, of taking up food particles, and probably of reproduction by fission.

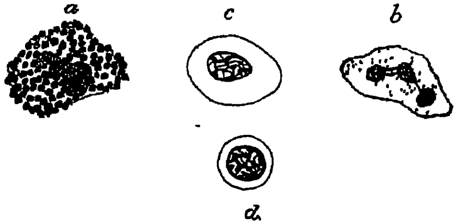
Several varieties of leucocytes exist in the blood. The most numerous variety, the 'polymorphonuclear' leucocyte, presents a nucleus which is lobed or composed of several parts united by fine threads. The protoplasm contains some very fine granules which have only a faint affinity for acid dyes such as eosin.

More sparse are the leucocytes known as 'hyaline.' These possess only a single round or oval nucleus, and their protoplasm is free from granules.

About 5 per cent. of the leucocytes present a mass of coarse highly refracting granules in their protoplasm. These granules stain intensely with eosin and other acid dyes, and are therefore designated eosinophile. The nucleus is lobed or reniform.

The fourth variety represented in the figure is the *lymphocyte.* This consists of a large round nucleus surrounded by a thin layer of hyaline protoplasm. It is derived from the lymphatic glands, and probably represents an immature form of the hyaline leucocyte.

FIG. 17

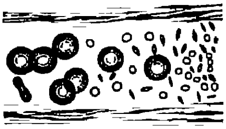


Various forms of leucocytes *a* Eosinophile corpuscle *b*. Ordinary polynuclear leucocyte ('neutrophile'). *c* Hyaline corpuscle. *d* Lymphocyte

Very rarely we find a fifth form of corpuscle containing granules which stain deeply with basic dyes, such as hæmatoxylin or methylene blue, and are therefore called *basophile.*

Besides the red and white corpuscles, a third formed element has been described under the name of blood-platelets. These are small bodies, disc-shaped or irregular, about one quarter the diameter of a red corpuscle, and are always to be observed on examining the blood immediately after it has left the body. They have also been called hæmatoblasts, on the assumption that they were precursors of the red blood-corpuscles. These platelets have been observed in normal circulating blood, but it seems probable that they may be added to by a process analogous to one of precipitation in the plasma as it commences to die or to cool down.

FIG 18.



Blood-corpuscles and blood-platelets, within a small vein (Schafer, after Osler.)

Chemistry of the Red Blood-corpuscles

We have already mentioned that these can be regarded as consisting of two parts, the hæmoglobin and the stroma, probably in a state of loose chemical combination.

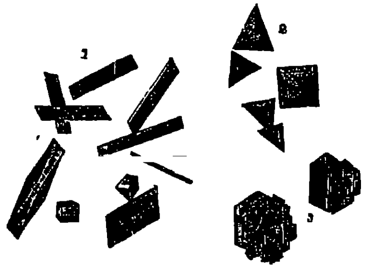
By various means it is possible to destroy this combination and to dissolve out the hæmoglobin, leaving the colourless, swollen-up stroma floating in the plasma. The effect of this is to make the blood darker but more transparent. In this condition it is spoken of as 'laky blood.'

Blood may be made laky by the following means:

(*a*) Addition of a small amount of ether.
(*b*) Free dilution with water.
(*c*) Alternate freezing and thawing.
(*d*) Addition of bile salts; and various other ways.

If this blood be allowed to stand in a cool place for an hour or two, a mass of crystals is deposited, which consist of oxyhæmoglobin. This crystallisation occurs very readily in the blood of some animals, such as the rat, guinea-pig, and dog; much less so in that of others, such as man, rabbit, and sheep.

FIG 19.



Crystals of oxyhæmoglobin. 1 From rat 2 From guinea-pig. 3 From squirrel

tablets of dark red

Oxyhæmoglobin thus obtained and purified by recrystallisation forms rhombic prisms or tablets of a dark-red colour (Fig. 19). It is a compound of a protein with an iron-containing residue (hæmatin), and is distinguished from all other proteins by the ease with which it crystallises. Its percentage composition probably varies slightly in different animals.

Elementary analysis of hæmoglobin crystals from the blood of the horse gave the following results:

	per cent.
Carbon	51·15
Hydrogen	6 76
Nitrogen	17 94
Sulphur	0·389
Iron	0·336
Oxygen	23 425

The empirical formula for hæmoglobin calculated from this would be—

$$C_{712}H_{1130}N_{214}O_{245}FeS_2.$$

The most important property of hæmoglobin is its power of uniting with a definite proportion of oxygen to form an easily dissociable compound, oxyhæmoglobin. One gram of hæmoglobin will combine with about 1·5 c.c. of oxygen (measured at 0° C. and 760 mm. pressure). This compound can be dissociated again by various agencies, such as heat or simple exposure to a vacuum, and we shall see, when talking of respiration, how very valuable to the organism is this easy dissociability of the oxyhæmoglobin molecule.

If carbon monoxide gas be led through a solution of oxyhæmoglobin, the oxygen is replaced by an equivalent proportion of CO, so that a more stable compound, CO-hæmoglobin, is formed; and this in its turn can be split up by nitric oxide gas with the formation of NO-hæmoglobin. Thus the order of stability of these three compounds would be—

NO-hæmoglobin
CO-hæmoglobin.
O_2-hæmoglobin

The poisonous properties of CO gas are due to this power it has of turning out the oxygen from the oxyhæmoglobin, thus depriving the tissues of the oxygen which is normally carried to them by the red corpuscles.

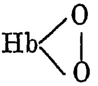
Oxyhæmoglobin is a brighter red and slightly less soluble than hæmoglobin. Solutions of the latter are dichroic, appearing green by reflected and bluish-red by transmitted light.

The reduction of oxyhæmoglobin to hæmoglobin is easily effected by various reducing agents, such as ammonium sulphide or Stokes' fluid (an alkaline solution of ferrous tartrate). This change in the colour of the compound is accompanied by a very evident change in its absorption spectrum.

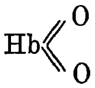
Dilute solutions of oxyhæmoglobin placed in front of the slit of a spectroscope give a very pronounced absorption spectrum, showing two black bands between Fraunhofer's lines D and E. On adding a few drops of Stokes' fluid to the solution and warming gently, these two bands disappear, and are replaced by a single band, rather fainter and broader than the O_2Hb bands, and situated between them. On shaking the solution up with air, the bands of O_2Hb return, only to disappear again when it is allowed to stand.

Carboxyhæmoglobin has a very similar spectrum to oxyhæmoglobin, but is a much brighter red. This difference in colour is best observed on diluting the blood, when oxyhæmoglobin acquires a yellowish tint, while the pink colour of CO-hæmoglobin is retained so long as any colour is visible. The most important distinction between the two kinds of blood lies, however, in the fact that CO-hæmoglobin is *unaltered* by the addition of ammonium sulphide or Stokes' fluid.

Another compound of hæmoglobin with oxygen is *methæmoglobin*. This substance, although not of normal occurrence in the body, is found in urine and in blood whenever there is a sudden breaking down of red corpuscles with the setting free of excess of hæmoglobin in the blood plasma. It may be prepared by the addition of potassium ferricyanide, permanganate, or other oxidising agent to the blood, or to a solution of hæmoglobin. It is a chocolate-brown substance, crystallisable, and gives a distinct absorption band in the red between the Fraunhofer lines C and D On treatment with a few drops of ammonium sulphide, the methæmoglobin is converted into hæmoglobin, and this on shaking with air will re-form oxyhæmoglobin. This reduction cannot be effected by simple physical means, such as exposure to a vacuum, and it seems probable that methæmoglobin contains exactly the same relative amount of oxygen as oxyhæmoglobin, but in a different state of combination, thus—



Oxyhæmoglobin



Methæmoglobin.

It is interesting to note that, on treating oxyhæmoglobin with potassium ferricyanide, the whole of its oxygen is given off in the free state, the ferricyanide only then attacking the reduced hæmoglobin and oxidising it again (but in a different way) to methæmoglobin.

This fact has been utilised by Haldane in devising an easy method for determining the oxygen capacity of any given sample of blood (i e the total amount of oxygen which the blood can hold in combination)

A measured quantity of arterial blood is placed in a bottle and laked by the addition of some weak ammonia A small tube containing potassium ferricyanide is then placed in the bottle, which is then closed and connected by a rubber tubing with a graduated gas burette containing water The bottle is then inverted so as to mix the ferricyanide solution with the blood All the combined oxygen of the oxyhæmoglobin is given off, and its volume determined by reading off the amount of water displaced in the gas burette. Care, of course, must be taken to keep the temperature of the whole apparatus constant during the operation

Hæmoglobin is very easily destroyed by various means (heat, alcohol, weak acids, and strong alkalies), being split up into an iron-containing pigment, hæmatin, and a protein residue, which is called *globin.* The latter can be prepared by treating the pure hæmoglobin with weak hydrochloric acid, which dissolves and splits up the hæmoglobin. The globin can then be precipitated by the addition of ammonia. Although coagulable by heat it presents many analogies with the group of proteins which have been described as *histones,* and can therefore be included for the present in this class.

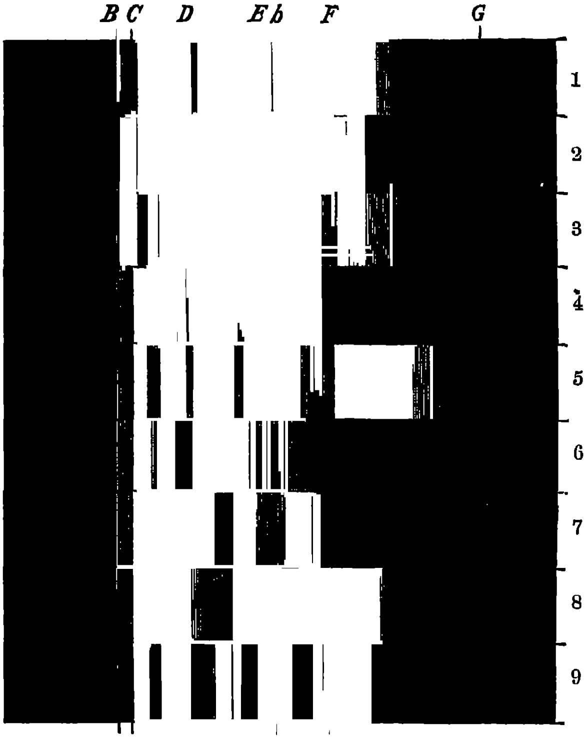
Hæmatin ($C_{32}H_{30}N_4O_3Fe$), when dried and purified, forms a bluish-black crystalline mass, insoluble in water and alcohol, but easily soluble in acids or alkalies in alcoholic or watery solutions. It forms compounds with acids and alkalies which are known as acid and alkaline hæmatin, each of which gives a characteristic absorption spectrum.

With hydrochloric acid it forms a crystalline hydrochloride known as *hæmin.* This compound is prepared with extreme ease, and this fact, combined with the very definite appearance of its crystals, renders it a very delicate test for blood.

To prepare hæmin crystals a little dried blood, hæmoglobin, or hæmatin is heated with a minute crystal of common salt and glacial acetic acid, and then allowed to cool. Hæmin crystallises out, and can be recognised on examination under the microscope. The crystals are dark brown, sometimes nearly black, and present the form of rhombic plates, often arranged in radiating bundles.

Alkaline hæmatin is interesting from the fact that it may be reduced by ammonium sulphide and re oxidised on shaking with air, just like a solution of O_2Hb. The spectrum of oxy-alkaline hæmatin shows one very indefinite absorption band close to D. Reduced alkaline hæmatin gives two sharp absorption bands, similar to those of oxyhæmoglobin, but rather nearer the blue end of the spectrum (Fig. 20).

Fig 20



Absorption spectra of hæmoglobin and its derivatives 1 Oxyhæmoglobin. 2 Reduced hæmoglobin. 3 Methæmoglobin. 4 Alkaline methæmoglobin. 5. Acid hæmatin in ether. 6. Alkaline hæmatin in rectified spirit 7. Reduced hæmatin 8 Acid hæmatoporphyrin 9. Alkaline hæmatoporphyrin (From MacMunn)

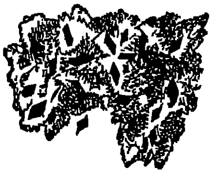
A body similar to, if not identical with, reduced alkaline hæmatin, *hæmochromogen,* is formed when hæmoglobin is warmed with caustic potash in a vessel from which all air has been driven out by the passage of a stream of hydrogen or other neutral gas.

If pure hæmin be treated with ammonium sulphide, it is reduced to hæmochromogen. If to this solution globin (prepared from hæmoglobin) be added, and the mixture allowed to stand for some days, it is found that reduced hæmoglobin is formed. It is interesting to note that egg-white may be used in this experiment instead of globin, showing that other proteins can take the place of globin in the hæmoglobin molecule.

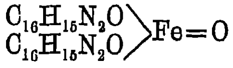
Other derivatives of hæmoglobin are—

a. Hæmatoporphyrin ($C_{16}H_{18}N_2O_3$), or iron-free hæmatin, is easily prepared by the action of strong sulphuric acid on blood, oxyhæmoglobin, or hæmatin, or by the action of 10 per cent. hydrochloric acid on reduced hæmoglobin, the separation of the iron from the rest of the molecule taking place with greater readiness in the absence of oxygen. It forms a deep purple solution with characteristic spectrum in the acid, from which it is precipitated as a black powder on free dilution with distilled water. It is isomeric with bilirubin. With alkalies it forms alkaline hæmatoporphyrin, with spectrum differing somewhat from the acid compound. Hæmatoporphyrin is found in minute traces in normal urine, but may occur in large amount in urine after poisoning by sulphonal. Hæmatin may be regarded as consisting of two hæmatoporphyrin groups linked together by means of one atom of iron, which also attaches an oxygen atom, as is represented by the formula

FIG. 21.



Hæmin crystals



$$\left.\begin{matrix}C_{16}H_{15}N_2O\\C_{16}H_{15}N_2O\end{matrix}\right\rangle Fe=O$$

b. Hydrobilirubin ($C_{32}H_{40}N_4O_7$) is produced by the action of tin and sulphuric acid on an alcoholic solution of hæmatin.

c. Hæmatoidin (probably identical with bilirubin) occurs as orange-red rhombic tables in old blood-clots in the body.

The STROMA may be obtained from laky blood by the addition of dilute sulphuric acid or acid sodium sulphate, by which the swollen-up stromata are shrivelled up; they may be collected by allowing the liquid to stand, or by means of the centrifuge. On chemical analysis they are found to consist chiefly of nucleo-proteins. They are soluble in weak alkalies, and on prolonged gastric digestion give an insoluble residue, rich in phosphorus (nuclein). On extraction with alcohol and ether they yield a certain amount of lecithin, cholesterin, and fats.

Important constituents of the red corpuscles are the salts and water The salts are chiefly potassium and phosphoric acid compounds, there being very little chlorides present, and little or no sodium (cf. the serum).

The corpuscles contain about two-thirds of their total weight of water.

Life-history of the Red Blood-corpuscles

There can be no doubt that a continual destruction of red blood-corpuscles is going on in the body. Thus an animal secretes every day by the agency of the liver a considerable amount of bile, containing a pigment, bilirubin. This pigment can be shown to be derived from the hæmoglobin of the red blood-corpuscles In cases where an effusion of blood has taken place into the brain or the connective tissues, we often find some months after the lesion that the corpuscles and red pigment have disappeared, and that the connective tissue in the vicinity contains a number of yellowish-brown crystals, known as hæmatoidin crystals. These crystals are identical in form, composition, and reactions with bilirubin, the colouring matter of the bile.

Under normal circumstances however, the conversion of hæmoglobin into bile-pigment, as we shall see later on, takes place exclusively in the liver. It is found that if, by the injection of poisons such as pyrogallol or toluylene diamine, a number of red corpuscles are broken up and destroyed, setting free hæmoglobin in the blood-plasma, there is marked increase in the amount of bile-pigment formed by the liver; and a similar increase may be brought about by the injection of solutions of pure hæmoglobin into the blood. What is the chemical change involved in this conversion ?

From a comparison of the formula of hæmatin ($C_{32}H_{30}N_4O_3Fe$) with that of bilirubin ($C_{16}H_{18}N_2O_3$), we see that the change is associated with a loss of iron ; and we find, as a matter of fact, that in all cases in which there is an increased *hæmatolysis* (destruction of red corpuscles), there is at the same time an accumulation of iron in the liver. This accumulation is especially well marked in cases of pernicious anæmia. It seems probable that, under normal circumstances, the hæmoglobin is broken up in the liver, part of the hæmatin molecule being transformed into bilirubin and turned out of the body with the fæces, while the iron is stored up in the liver to assist in the formation of fresh hæmoglobin or new red blood-corpuscles.

The presence of iron in the liver cells may be easily demonstrated in fresh or alcohol-hardened specimens by treating a cut surface or section successively with potassium ferrocyanide and dilute hydrochloric acid After severe blood destruction the whole liver may present on this treatment a deep-blue colour, due to the formation of iron ferrocyanide

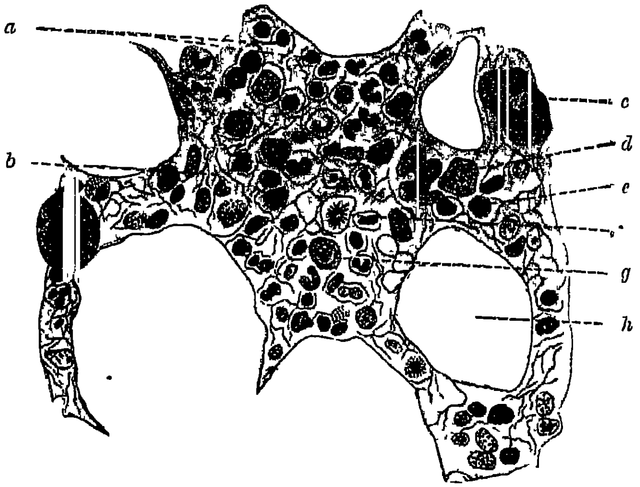
We have not yet been able in the laboratory to convert hæmatin directly into bilirubin. Iron-free hæmatin or hæmatoporphyrin is however very nearly allied to bilirubin, the empirical formulæ of these two bodies being identical. We can moreover by the action of reducing agents obtain identical products from hæmatin and bilirubin. Thus by treating hæmatin with tin and hydrochloric acid or by acting on bilirubin with sodium amalgam, a body, hydrobilirubin, is produced, which apparently belongs to the same class of bodies as urobilin, a pigment occurring in small quantities in the urine. There is no doubt that this latter pigment can be derived from bilirubin under the influence of putrefactive organisms, and it is in this way that the urobilin of the fæces (the so-called stercobilin) is produced.

It is evident then that the pigments excreted from the body in the urine and fæces are derived from hæmatin, and therefore that a disintegration of the red blood-corpuscles must be continually taking place.

Since, in a healthy animal, the amount of corpuscles in the blood remains approximately constant, a continual production of new corpuscles must go on to take the place of those destroyed and discharged to form bile and urinary pigments. There is considerable doubt as to the exact mode and place in which this regeneration occurs, and the process seems to be quite different according as we consider the fœtal or adult condition. We may therefore consider first the formation of red corpuscles in the embryo and new-born animal.

The red corpuscles at an early stage of fœtal life are nucleated, like those of the frog or bird. In the vascular area of the chick, nests of nuclei are found embedded in colourless masses of non-differentiated protoplasm. A little later it is seen that these nuclei are all surrounded with a differentiated portion of the protoplasm, which now contains hæmoglobin, the intervening undifferentiated portions having become more fluid and representing the future blood-plasma. Very soon the masses of protoplasm become channelled and connected with one another and with the large vessels coming from the heart, and the fully formed blood moves on into the general circulation in response to the heart-beat.

FIG. 22

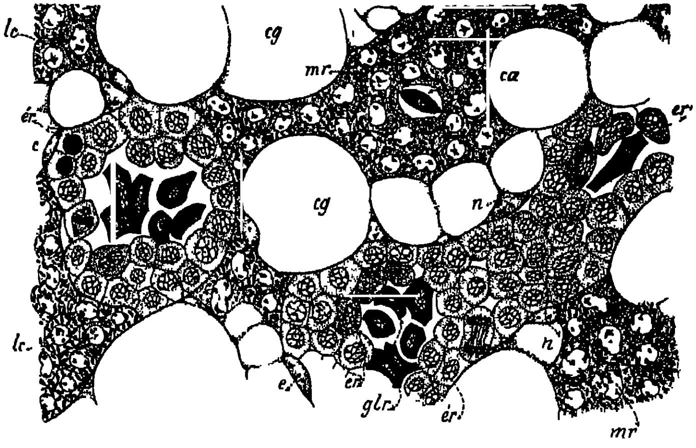


Section of red marrow of mammal (Bohm and Davidoff) *a*, *e*, erythroblasts, *b*, reticulum, *c*, myeloplax; *d*, *g*, marrow cells, *f*, a marrow cell dividing, *h*, a space which was occupied by fat

According to Schafer, non-nucleated blood-discs may be produced in a very similar fashion. Towards the end of fœtal life we find in the developing connective tissue branched masses of protoplasm containing nuclei. These nuclei however are not wasted on mere oxygen carriers but are entirely used to form the endothelium of the capillary wall; and non-nucleated red corpuscles are developed by a simple differentiation of the central part of the protoplasmic mass, the parts of the protoplasm between the corpuscles again appearing to furnish the material for the fluid plasma.

This process however seems to come to an end within a few days after birth. In order to find the seat of blood production after this period, the best method is to increase the activity of the process by inducing an abnormally large destruction of corpuscles, either by the injection of poisons or by the actual removal of blood. If the animal be killed when by such means its blood-forming powers have been called upon to the utmost, the only organ or tissue of the body which exhibits any sign of hypertrophy is the red marrow of the bones. Ordinarily in the adult animal this red marrow is found occupying only the spaces of the cancellous tissue of the ribs and vertebræ, and at the ends of the long bones. But after bleeding it may be found occupying a large extent

FIG 23.



Section of red marrow of pigeon (Denys). *lc*, eosinophile leucocytes, *cg*, fat cells, *e*, nucleus of endothelial cell of blood-vessel, *ca*, blood capillary, *er*, erythroblasts lying within vascular endothelium; *glr*, fully formed red corpuscles of the shafts of the bones. On microscopic examination it is found that, of the numerous cells which compose this tissue, myelocytes, osteoblasts, marrow and fat cells, the only elements present in excess are nucleated cells containing hæmoglobin in their protoplasm. Many of these cells are in a state of active division, and all intermediate stages can be found between the daughter-cells, containing well-formed nuclei and stained with hæmoglobin, and the ordinary non-nucleated red blood-disc, the nuclei apparently degenerating and undergoing solution or extrusion from the cell. The capillaries in the red marrow are bounded by walls which may be imperfect, thus admitting the entry of the newly formed corpuscles into the circulating blood. According to some authorities, the large red cells are themselves derived from colourless nucleated cells, the so-called erythroblasts. Among the complex of cells forming the red marrow it is very difficult to make certain of this fact, but there seems to be little doubt that such is the case in the bird. If we examine the red marrow of the pigeon we find that the capillary walls are perfect, but are lined internally by a layer of blood-forming cells (Fig. 23). In this layer all stages can be found between the colourless erythroblast and the mature oval nucleated red blood-corpuscle, which is characteristic of this class of animals.

The occasional occurrence of nucleated red blood-corpuscles in the spleen, especially after great loss of blood, has been regarded by some physiologists as a proof that this organ also takes part in blood formation. It seems more probable that the chief function of the spleen in this regard consists in the destruction by its cells of inefficient or weakened corpuscles, and that it is rather a blood-destroying than a blood-forming organ.

We need at present only mention the view put forward by Hayem and others that the red blood-discs are produced in the circulating blood by a gradual modification of the blood-platelets or hæmatoblasts

We have no evidence to tell us how long a red corpuscle lives, or how long it can carry on its functions before it is broken up in the liver or spleen and cast out of the body. Experiments, such as injection of the blood of a bird into a mammal when the introduced blood-corpuscle can be always identified, naturally give us no idea of the duration of activity of a normal corpuscle.

Since iron is an essential constituent of hæmoglobin, it is evident that our food must contain enough iron to restore the loss of it in the corpuscles. The amount however need be only very small if it were all assimilated, for the whole blood of an average-sized man does not contain more than about 2·5 grms. Fe.

Inorganic forms of iron, such as the iron salts, are however absorbed only in very small quantities, and there is some probability that a good deal of the hæmoglobin is reintegrated from an organic form of iron contained in the food, called hæmatogen—a protein belonging to the group of nucleo-proteins and containing iron in a state of intimate chemical combination. After administration of organic iron salts, this metal may be demonstrated in the absorbing villi of the intestine. It is difficult however to determine exactly the amount of iron absorbed, since the main channel for excretion of this substance, as for most of the other heavy metals, is the intestinal tract. Thus the amount of iron which can be recovered from the fæces is no index to the amount of iron which has escaped absorption.

Chemistry of White Blood-corpuscles

The chemistry of the white blood-corpuscles is the same as that of any indifferent animal cells. It can be studied most conveniently on the leucocytes of lymphatic glands. These are found to consist almost entirely of bodies belonging to the class of nucleo-proteins. The extract of these cells on treatment with acetic acid gives a precipitate of nucleo-protein, which is soluble in weak alkalies. The solution produces intravascular clotting on injection into the blood-vessels. Besides the nucleo-proteins, the leucocytes contain lecithin, fats, and cholesterin, and often glycogen, in addition to various nitrogenous extractives. Their salts are similar to those of the red corpuscles, and contain a preponderance of potassium salts and phosphates.

Origin of White Blood-corpuscles

The various kinds of leucocytes probably differ in their mode of origin. There seems little doubt that the hyaline corpuscles are derived from the lymphocytes, which are found in the lymphatic glands and enter the blood with the lymph-stream by way of the thoracic duct.

Many authorities ascribe a similar mode of origin to the chief or polynuclear leucocytes. These corpuscles occur mainly in the blood, and have been seen in a state of division, so that it is most probable that they reproduce themselves by direct cell division in the blood-stream itself.

The eosinophile corpuscles are found in large numbers in the connective tissue in various parts of the body, especially in the red marrow of bones. They probably represent a migratory tissue *sui generis* (perhaps of a glandular nature), and are derived from similar cells by division in the blood-stream or in the connective tissues.

Estimation of Blood-corpuscles

In order to count the corpuscles, a known small volume of blood is diluted with some indifferent fluid (such as 0·9 per cent NaCl solution), and a drop of this placed in a small cell on a glass slide, the bottom of which is ruled with squares. The depth of the cell and the size of the squares being known, it is easy to count the corpuscles lying on each square under the microscope, and from this to estimate the number present in a cubic millimetre of undiluted blood.

Thus in Gowers' hæmocytometer the graduated glass cell is $\frac{1}{5}$ millimetre deep, and each square is $\frac{1}{10}$ millimetre each way.

Five cubic mm of blood are drawn into a graduated capillary tube, and then blown into a 'mixing vessel' containing sodium sulphate solution (sp. gr. 1025). The mixture is well stirred and a drop placed in the middle of the cell, and the cell covered. In a few minutes the corpuscles have sunk to the bottom of the cell, and rest on the squares. The number of corpuscles in ten squares is counted, and this multiplied by 10,000 gives the number of corpuscles in a cubic millimetre. In normal blood there are from four to five million corpuscles in a cubic millimetre (*i.e.* an average of forty or fifty to each square of Gowers' instrument).

Estimation of Hæmoglobin

To estimate the amount of hæmoglobin in a given sample of blood, 20 cubic mm are taken and diluted with water, until the mixture is equal in tint to a permanent standard coloured solution made with glycerin and carmine, and corresponding in tint to blood diluted 100 times (Gowers' hæmoglobinometer). Thus the number of times the blood must be diluted to bring it to a standard tint divided by 100 gives the percentage amount of hæmoglobin present, the normal amount being taken as 100.

In von Fleischl's hæmoglobinometer the specimen of blood is always diluted to the same extent, but the standard of comparison is a wedge of coloured glass, which can be slipped to and fro till its tint exactly equals the tint of the sample of diluted blood placed in a glass cell by the side of the wedge for comparison. The sliding wedge is graduated to indicate the percentage amount of hæmoglobin present compared with the normal. Thus if the tint of the blood is equal to the wedge at 100, the blood contains the normal amount of hæmoglobin; if at 50, half that amount; and so on.

SECTION 2

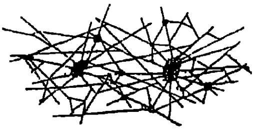
THE COAGULATION OF THE BLOOD

The most striking property of blood is that of clotting when it is shed. If blood be drawn from an artery or vein into a vessel, in from two to three minutes it becomes rather viscid. This viscidity increases till the whole mass of blood solidifies to form a jelly-like mass, exactly occupying the volume of the original fluid blood.

After about an hour, yellowish drops exude from the surface of the clot, and this exudation continues till the clot has shrunk to half its former dimensions, and floats in a clear yellow fluid (the serum).

Thus, as a result of standing, the blood has been resolved into solid clot and fluid serum On examining the clot under the microscope, we find that it consists of all the corpuscles enclosed in a meshwork of fine fibrils (Fig. 24).

FIG 24



Network of fibrin, after washing away the corpuscles from a film of blood that has been allowed to clot, many of the filaments radiate from little clumps of blood-platelets (Schafer)

If however, directly the blood is drawn, it be whipped with a bundle of twigs or anything presenting a large rough surface, the latter becomes covered with a stringy mass, and we find that the blood has lost its power of setting to form a jelly. This stringy mass is called fibrin, and it is evident that the coagulation of the blood is due to the appearance in it of these fibrils of fibrin, which form a network enclosing in its meshes the corpuscles and the remaining fluid part of the blood. This network then contracts, squeezing out the fluid, which appears on the surface of the clot as the serum.

Fibrin obtained by whipping fresh blood, or by washing away the corpuscles from a clot, exhibits the following properties:

It is insoluble in water or in dilute saline solutions. In stronger solutions, such as 10 per cent. potassium nitrate, it is very slowly dissolved, but is altered in the process, the solution containing not fibrin but proteins belonging to the globulin class. It swells up in dilute HCl (0·2 per cent.), and if digested with it at a temperature of 40° C. slowly dissolves, with the formation of acid albumen or syntonin. If shreds of fibrin are suspended in water and heated to boiling, they are converted into coagulated protein, losing the property of swelling up in dilute HCl. The general reactions and constitution of fibrin show that it belongs to the class of proteins.

The serum, the other end-product of the reactions which determine coagulation, is a transparent yellowish fluid, containing about 7 to 9 per cent. total solids. Of these, nearly eight parts are protein in nature. Proceeding on the lines of the conventional classification laid down in the second chapter, we may separate two distinct proteins in the serum—serum-globulin or paraglobulin, and serum-albumen. The serum-globulin may be thrown down by saturation with magnesium sulphate, or by adding to the serum an equal volume of a saturated solution of ammonium sulphate. It is also thrown down if the serum be dialysed against distilled water, showing that it is insoluble except in the presence of a certain amount of neutral salt.[1] On heating, it coagulates at about 75° C. An imperfect separation of paraglobulin may be effected by diluting the serum with twenty volumes of distilled water, and adding a trace of acetic acid or passing a stream of CO_2 through the liquid. On removing the globulin precipitate, the filtrate still contains 3 to 5 per cent. of a protein belonging to the albumin class, known as serum-albumen, which is soluble in distilled water, not precipitated by saturation with magnesium sulphate, but totally precipitated on saturating with solid ammonium sulphate. The filtrate from this last precipitate is perfectly free from proteins. Solutions of serum-albumen coagulate on heating between 77° and 85° C.

By the method of fractional heat-coagulation three varieties of serum-albumen have been separated But in the absence of further chemical proof the value of the separation so effected must be regarded as doubtful

---

[1] It has been shown lately that the precipitate obtained from serum on saturation with $MgSO_4$, or half saturation with ammonium sulphate, really comprises two bodies —

(*a*) A true globulin, called euglobulin, insoluble in pure water, and identical with the precipitate obtained on dialysis

(*b*) A pseudo-globulin, soluble in distilled water, and therefore remaining in solution when the salts are removed by dialysis

The other constituents of the serum include extractives such as urea, sugar (in small traces), and about 1 per cent. inorganic salts, of which sodium chloride, carbonate, and phosphate are the most important.

We have now to consider the processes which lead to the formation of fibrin in shed blood. In order to analyse these processes it is necessary to slow the process of coagulation.

Clotting is favoured by the following influences.

Exposure to high temperature (up to 50° C).

Contact with foreign surfaces (as when the blood is whipped with a bundle of twigs).

It is retarded or prevented by—

Exposure to cold (blood may be kept fluid almost indefinitely at a little above 0° C.).

Mixture with various salts, such as magnesium or sodium sulphate, or common salt. The blood is received into one-third its volume of a saturated solution of magnesium sulphate, or into an equal volume of half-saturated sodium sulphate solution.

By receiving the blood from the vessels directly into a solution of a soluble oxalate in such proportions that the resulting mixture contains 1 in 1,000 of oxalate.

Injection of albumoses ('peptone') or of leech extract (also an albumose) into the veins before the blood is drawn.

Contact with the lining membrane of a living blood-vessel. Thus if we ligature the jugular vein in a horse at two points, the blood in the intervening part will remain fluid for many hours. In fact, two such 'living test-tubes' may be prepared, and the blood poured in a thin stream from one to the other without coagulating.

If blood be drawn from an artery or vein in a bird, without coming in contact with the surrounding tissues, it does not clot. Clotting can be at once induced by adding a small fragment of tissue, or a watery extract of any of the bird's tissues.

If blood which has been prevented from coagulating by one of these methods be allowed to stand in a cool place, the blood-corpuscles, which are heavier than the plasma, gradually sink to the bottom, leaving a clear supernatant layer of plasma, which can be pipetted or siphoned off.[1]

---

[1] This process is much shortened by using a centrifugal machine This consists essentially of a horizontal wheel, with slots cut in it in which tubes are

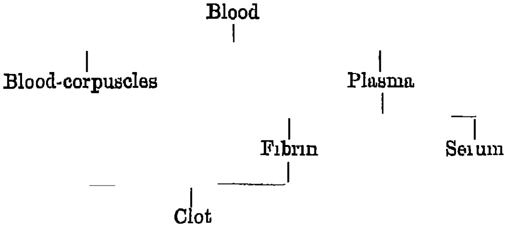
Plasma prepared in this way perfectly free from formed elements can be easily made to clot. Cooled plasma clots directly its temperature is allowed to rise; salt plasma on simple dilution; oxalate plasma on the addition of a soluble salt of lime, peptone plasma on dilution and passage of a current of CO_2.

The clot formed is colourless, and contracts after formation just like the clot formed in the whole blood. It only differs from the latter in containing no corpuscles: in fact it is pure fibrin.

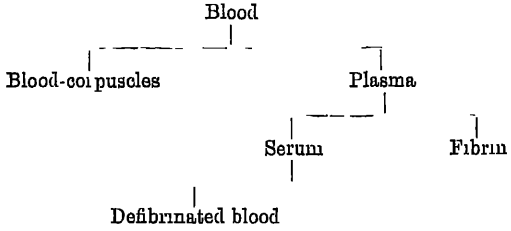
Hence it is evident that the *blood-plasma contains within itself the precursors of fibrin.*

We may therefore represent the processes occurring in coagulation schematically as follows:

Clotting of blood at rest



Clotting of whipped blood



What are these precursors? If plasma prepared in either of the foregoing methods be saturated with common salt, a sticky white precipitate is produced. This may be collected on a filter and washed with saturated salt solution to remove all traces of adhering plasma. If we dissolve this substance

---

suspended. These tubes are filled with the blood, and the wheel made to revolve about 2,000 times per minute The tubes swing out to a horizontal position, and the centrifugal force causes all the heavier particles to collect at the ends of the tubes, so that in half an hour the blood-corpuscles form a compact mass at the bottom of the tubes in dilute salt solution, the solution (at the ordinary temperature) soon becomes viscid and clots, the clot after a while contracting and separating out a serum, which is found to contain a protein belonging to the globulins. Denis, the discoverer of this precipitate, called it *plasmine*, and supposed that clotting consisted essentially in a splitting up of this simple soluble body into two bodies, one of which was insoluble (fibrin) and the other soluble (serum globulin).

Later on Alexander Schmidt found it possible to separate this plasmine into two substances, which he called fibrinogen and fibrinoplastin. Now the latter is identical with the paraglobulin of the serum, and this, as Hammarsten showed, takes no part in the process of clotting. We must therefore regard the fibrinogen as the precursor of fibrin, since it entirely disappears and is replaced by fibrin.

Fibrinogen was originally prepared by passing a current of CO_2 through plasma after dilution with twenty volumes of water. The separation, however, is much better effected by a modification of Denis' original method. Sodium chloride is added to the plasma until it reaches 15 per cent. This is conveniently done by adding to each volume of the plasma an equal volume of a saturated solution of NaCl, containing about 30 per cent. of the salt. A precipitate is gradually produced, at first granular and then becoming flocculent and fibrinous. This precipitate may be washed free from adherent protein by half-saturated solution of sodium chloride. The pure fibrinogen thus obtained belongs to the class of globulins, being insoluble in distilled water but soluble in dilute salt solutions. The solutions coagulate on heating at the low temperature of 56° C.

If the plasma which served as the source for the fibrinogen was sodium sulphate or sodium chloride plasma, the solution of the fibrinogen may clot on simple standing, being almost entirely converted into fibrin, only a small trace of protein being left in solution. The change therefore from fibrinogen to fibrin involves a process of splitting, in which by far the larger proportion becomes insoluble. If however we get the fibrinogen from magnesium sulphate or oxalate plasma, the solution, although in all other respects identical with that obtained from sodium sulphate plasma, does not clot on standing; and the same is sometimes found with the fibrinogen solution from sodium sulphate plasma, if the precipitated fibrinogen has been very thoroughly washed. In all cases however a pure fibrinogen solution can be made to clot by adding to it a drop or two of serum, or of the washings of a blood-clot. It is evident therefore that some other factor besides fibrinogen must be present in order to bring about coagulation. Since this other factor may be in excessively small quantities, and may, if given time, convert almost indefinitely large amounts of fibrinogen into fibrin, it has been regarded as a ferment, and called *fibrin ferment*.

A fairly pure solution of the fibrin ferment may be prepared in the following way. Serum, or chopped-up blood-clot, is allowed to stand with about twenty times its volume of absolute alcohol for two or three months. The proteins by this means are precipitated and rendered insoluble in water, so that an aqueous extract of the dried precipitate contains very little protein matter, but is rich in fibrin ferment; that is to say, it possesses the power of converting solutions of fibrinogen into fibrin, for we can never recognise ferments except by their action.

We must conclude therefore that *the coagulation of the blood is due to the conversion of a soluble protein present in the plasma—fibrinogen, into an insoluble protein—fibrin, under the agency of a ferment, which is known as fibrin ferment or thrombin.*

As to the chemical nature of the ferment we know practically nothing It is destroyed on heating to 55° C, and is always associated with a certain amount of protein It is stated by some authors, on rather insufficient grounds, to belong to the class of nucleo-proteins

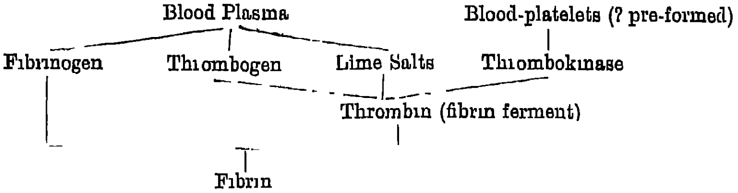
What is the origin of this fibrin ferment? It is not present in the circulating blood, but is formed after the blood has left the vessels. If blood be received straight from an artery into a large quantity of absolute alcohol, and the precipitate extracted with water after two or three months, the extract is not found to have any power of causing clotting in solutions of fibrinogen.

Schmidt was of opinion that the colourless corpuscles break down as soon as they leave the vessels and liberate the ferment. If horse's blood be received into a vessel placed in ice, and allowed to stand, it soon separates into three layers: an upper layer of pure plasma, a thin layer of leucocytes and granules, and a layer of red corpuscles. If the temperature of the blood be allowed to rise, it clots throughout, but the clotting begins soonest in the layer of leucocytes, and is firmest there. If the clot be divided into three portions, and treated for the extraction of ferment, the extract from the part of the clot enclosing the leucocytes and granular matter is much more active than that from either of the two ends of the tube. Of course the significance of this experiment depends on the view we take of the origin of the granular matter. Schmidt looked on it as the *débris* of exploded corpuscles, while Wooldridge regarded it as a precipitate produced by the effect of cold on the plasma. This latter observer therefore considered that the ferment was produced, not from the leucocytes but from the plasma, and that the granular precipitate represented the precursor or zymogen of the ferment. Later researches by Hammarsten on the clotting of oxalate plasma have confirmed this view and thrown light on the necessary conditions of the change from precursor to ferment. Oxalate plasma will clot on the simple addition to it of a soluble salt of lime, *e.g.* $CaCl_2$, and the same statement holds good for the fibrinogen prepared from this plasma by the ordinary methods. If however the plasma be cooled to 0° C. for two or three days, a granular discoid precipitate is produced, and on separating off the plasma and extracting from it the fibrinogen, it is found that the solution will no longer clot with lime salts, but needs the addition of fibrin ferment. No effect is produced by adding the precipitate to the fibrinogen, *but if a little calcium chloride be mixed with the precipitate and the mixture added to the fibrinogen solution, clotting ensues.* This shows that plasma contains in solution a precursor of fibrin ferment which has been termed *prothrombin*, the conversion of prothrombin into thrombin being dependent on the action of calcium salts. The origin of fibrin ferment is however rather more complex. Oxalate plasma, which has been separated from the precipitate of 'prothrombin,' can be made to coagulate by the addition of extracts of almost any animal tissues together with lime salts, and these were therefore supposed to contain prothrombin similar to that obtained by cooling oxalate plasma. But these extracts, even on mixture with calcium salts, are found to be without effect on pure solutions of fibrinogen. Moreover, the precipitate produced by cold, if thoroughly washed before treatment with lime salts, loses its power of evoking coagulation in fibrinogen solutions. It is therefore concluded that three factors are necessary for the production of fibrin ferment or thrombin, viz.: (1) lime salts; (2) a substance present in the precipitate of 'prothrombin' as well as in most animal tissues (this is called *thrombokinase*); (3) a substance present in solution in oxalate plasma, and carried down adhering to the precipitate obtained on cooling, which is called *thrombogen.*

Our present views as to the essential nature of the processes concerned in coagulation may be summed up as follows:—

When blood leaves the vessels there is a disintegration of the blood-platelets (themselves perhaps derived from antecedent changes in the plasma or from an unstable form of leucocyte) with a liberation of thrombokinase. This acts upon thrombogen, already in solution in the plasma, and in the presence of lime salts gives rise to thrombin. Under the influence of the ferment thrombin, the fibrinogen present in the plasma is transformed into fibrin.

These changes may be represented by the following schema:



This view of the nature of the changes involved in coagulation is borne out by observations on other forms of plasma, especially of plasma obtained from birds' blood This, when obtained with scrupulous cleanliness, so as to avoid any contamination with dust or with the tissues, remains permanently uncoagulable In the plasma got by centrifuging the blood, no blood-platelets are to be seen and no precipitate is produced by exposure to a temperature of 0° C. We may say therefore that blood-platelets, with their contained thrombokinase, are absent from birds' blood, and with them the property of spontaneous coagulability The blood is also free from fibrin ferment, but contains thrombogen as well as soluble lime salts It is only necessary therefore to add thrombokinase, in the shape of a watery extract of any tissue or cells, in order to cause the formation of thrombin and the conversion of the fibrinogen already present into fibrin

Intravascular Clotting

If fibrinogen be really present as such in the circulating blood, one would expect to produce intravascular clotting by the injection of solutions of fibrin ferment. We find however that with our ordinary thrombin solutions practically no effect is produced. If, however, the very strong fibrin ferments contained in some snake venoms be injected, universal intravascular clotting (thrombosis), may be produced. On the other hand, injection of solutions containing thrombokinase causes at once clotting of the blood in the vessels. This is probably the explanation of the action of the extracts of cellular tissues, containing the so-called tissue-fibrinogens.

A solution, tissue-fibrinogen, is prepared by extracting chopped-up thymus or lymphatic glands with water or normal salt solution After separating the suspended cells by means of a centrifuge, the clear fluid is treated with acetic acid; this throws down a precipitate of tissue-fibrinogen, which may be dissolved in 1 per cent. solution of sodium carbonate. A few c c of this solution, injected into the jugular vein, causes extensive intravascular clotting within 30 seconds of the beginning of the injection. In the rabbit intravascular clotting is practically universal, and this is also the case in the dog if in full digestion. In the fasting dog the clotting may be limited to the portal area In this case the rest of the blood, when drawn off, is found to be incoagulable. We may thus distinguish two phases in the action of tissue-fibrinogens on the living blood. first, a phase of increased coagulability, resulting in the production of a clot—the positive phase; secondly, a negative phase of diminished coagulability. If the injection be carried out very slowly, or the solution be dilute, only the negative phase may be produced. Subsequent injections, however rapid, of a strong solution have no effect, the animal being for the time protected or rendered immune by the first injection.

Certain histological observations support the view that coagulation is normally inaugurated by the disc-like precipitate of prothrombin, which appears to be identical with the blood-platelets of histologists. If a small vessel be observed under the microscope, and a small part of the lining endothelium injured, it is noticed that blood-platelets are deposited on the injured spot, so as to form a little heap. The platelets seem to fuse into one another, and finally form a little white mass of fibrin (white thrombus), which effectually occludes any opening in the wall of the vessel. This process in the living body always occurs when a vessel is injured, and is a means by which the animal is protected from bleeding to death from any small wound.

It may be well here to summarise the conditions which determine the clotting of the various kinds of plasma that have been mentioned in this section

1 Cooled horse's plasma contains all the fibrin precursors, and clots on simple rise of temperature If however it be cooled for some time and filtered, the thrombokinase is separated, and the filtered plasma will not clot without the addition of fibrin ferment

2. Sodium sulphate and sodium chloride plasma also contain all the fibrin

precursors and clot on simple dilution, the salt appearing merely to inhibit the action of the ferment on the fibrinogen Magnesium sulphate however gradually precipitates the thrombokinase and thrombogen The plasma prepared by the use of this salt contains therefore only fibrinogen, and needs the addition of fibrin ferment as well as dilution to make it clot

3 Oxalate plasma, when fresh, contains fibrinogen, thrombokinase and thrombogen It needs therefore only the addition of lime-salts If however it be cooled and filtered, the thrombokinase is separated, and to induce clotting, either fibrin ferment or a mixture of thrombokinase (or a tissue extract) and lime-salts must now be added.

4 Peptone plasma presents many peculiarities, and it is still doubtful how far the facts gained from its study are applicable to the explanation of the coagulation of blood under normal conditions The mere addition of peptone (*i e* a mixture of albumoses, especially hetero-albumose) to blood does not delay clotting It is necessary to inject the peptone in the proportion of 0 3 grm per kilo body-weight into the veins of a living animal (dog) It seems that, under the influence of the peptone, the liver cells or vascular endothelium secrete into the blood a substance which hinders clotting, so that the loss of coagulability is merely a secondary result of the peptone injection Peptone plasma resembles intravascular plasma in that it will clot only on addition of thrombokinase or tissue fibrinogens, and is unaffected by fibrin ferment It apparently contains not only a precursor of fibrin ferment, but also a precursor of fibrinogen, since it yields no precipitate on heating to 56° C, although, by precipitation with salt and re-solution, the typical fibrinogen described above results.

5 Leech-extract plasma can be obtained by injecting a decoction of dried leeches into the circulation, or by adding it to the blood as it leaves the vessels. The active principle of the decoction is a body allied to an albumose, which is secreted by the buccal glands of the leech, and which has the property of neutralising and so destroying the action of fibrin ferment.

Main Points in the Composition of the Blood

Specific gravity of whole blood about 1055, of corpuscles about 1085; of serum about 1035.

The specific gravity of the blood may be estimated clinically in the following way —A series of mixtures of glycerin and water are prepared, with specific gravities varying from 1030 to 1070 A drop of blood is then sucked up into a capillary pipette with its point bent to a right angle, and minute portions of this drop are expelled into a series of glasses containing glycerin and water mixtures of various strengths. The red drop expelled from the pipette will rise or sink in the fluid so long as its specific gravity differs from that of the fluid The specific gravity of the mixture in which the blood neither rises nor sinks is equal to that of the blood, and is the number we want to know

The blood is slightly alkaline.

This is best demonstrated by placing a drop on a piece of delicate glazed litmus-paper, and then wiping it off The spot where the blood rested is found to be stained blue

Blood contains from one-third to half its weight of corpuscles. The plasma is resolved by clotting into serum and fibrin. The serum contains in 100 parts—proteins (consisting of serum albumen and paraglobulin) 8 parts, salts about 1 part, water about 91 parts.

The paraglobulin and serum albumen occur in varying proportions. The proportion of paraglobulin to albumen in one case was 1 : 1·5 (man).

The chief salt present is sodium chloride, which constitutes 60 per cent. of the ash. Next to this comes sodium carbonate (about 30 per cent.), and besides these two we find traces of potassium, sodium, and calcium chlorides and phosphates. Traces of fats, cholesterin, lecithin, dextrose, urea, and other nitrogenous extractives are constantly found in the serum. The fats are much increased after a meal rich in them, and may give the serum a milky appearance.

The red corpuscles contain in 100 parts—water 70 parts, solid constituents 30 parts.

Of the solid constituents, hæmoglobin forms nine-tenths; the other tenth corresponds to the stroma, consisting of nucleo-protein, lecithin and cholesterin, and salts. There is a striking contrast between the salts of the corpuscles and those in the serum; the former consisting chiefly of potassium phosphate, the latter of sodium chloride, which may be almost or entirely wanting from the corpuscles.

The Biological Significance of certain Constituents of the Serum.

It has long been known that the serum of some animals acted as a poison when injected into others, producing extensive breaking up of corpuscles, appearance of hæmoglobin in solution in the urine, and death. The same destructive effect of serum on foreign corpuscles may be observed *in vitro*. Thus dog's serum causes a rapid destruction of the red corpuscles when added to defibrinated rabbit's blood, although there is no appreciable difference between the concentrations of the sera of the two animals This relative *globulicidal* action of the serum may be artificially produced. Thus injection of the corpuscles of a guinea-pig into a rabbit causes the serum of the latter to become globulicidal for the corpuscles of the guinea-pig. The globulicidal property is destroyed on heating the serum to 55° C.

The globulicidal or *hæmolytic* power of the serum depends on the presence in the latter of two distinct substances, viz an *antibody* or *amboceptor*, and a *complement*. Thus when rabbit's serum is made hæmolytic for guinea-pig's corpuscles, by repeated injections of the corpuscles of the latter into the rabbit, the amboceptor in the rabbit's serum is the direct result of the injection It is found that, if this serum be heated to 55° C, it loses its hæmolytic properties. These, however, are at once restored to it on the addition of some blood-serum from a normal guinea-pig It is therefore concluded that serum normally contains a substance, toxic for corpuscles, which is destroyed at 55° C This however is unable to act except in the presence of another substance, the immune body or amboceptor, which is specific for each kind of corpuscle, and is produced as the direct result of the injection of any foreign corpuscles into an animal The amboceptor is not destroyed at 55° C.

The blood sera of various animals have in the same way a destructive power on certain bacteria, and this action may be increased by the previous injection into an animal of the bacteria in question. It is by the development of such bactericidal substances that the animal is in many cases enabled to react to an infection, or to develop an immunity after one attack from further attacks of the disorder.

This reaction, viz. the production of 'antibodies' in the serum, is not confined to the effects of injecting living corpuscles or bacteria. Almost any protein, injected into an animal's veins, evokes the production in the animal of an antibody, a *coagulin*, which has the property of inducing a precipitate in solutions of the protein which had been injected, but in no other. The antibody therefore in this case is specific. In the same way the injection of toxins, the poisonous products of bacteria, *e.g.* diphtheria toxin, or tetanus toxin, causes the development in the blood serum of a corresponding antitoxin, which has the power of combining with and neutralising the toxin in question. This fact is made use of in therapeutics. Horses are injected with increasing doses of diphtheria toxin. After some time they are bled, and the blood serum so obtained, when injected into a patient the subject of diphtheria, neutralises the poison circulating in the body, and leads in this way to arrest of the disease.

Thus we must conclude that the serum of any individual, besides the definite chemical substances already described, contains a large number of 'antibodies' of complex constitution, which have been produced by the entry into the blood of bacterial poisons from without, or of ferments from the alimentary canal, or of proteins from the disintegration of tissues, and that these substances play an important part in the defence of the individual against further infection or spread of any process of destruction.

CHAPTER IV

THE CONTRACTILE TISSUES

Section 1

GENERAL CHARACTERS OF MUSCLE

The means by which the organism acts on its environment is furnished by the contractile tissues, under which term we include all the varieties of muscle, striated and unstriated.

All movements that require to be sharply and forcibly carried out are effected by means of striated muscular tissue, and as these movements are in nearly all cases under the control of the will, the muscles are often spoken of as *voluntary*.

Unstriated muscular fibres (often termed involuntary[1]) form sheets or closed tubes surrounding the hollow viscera, and by their slow prolonged contractions serve to maintain and regulate the flow of the contents of these organs.

Intermediate in properties between these two classes we find heart muscle; this, though striated, presents important histological differences from striated voluntary muscle. We shall study this form more fully when we come to consider the physiology of the whole vascular system.

The properties of the contractile tissues have been most fully investigated in voluntary muscles, the most highly differentiated members of the group; we shall therefore consider this part of the subject at length, merely indicating at the end in what points the unstriated involuntary muscles differ from the striated.

Voluntary Muscle

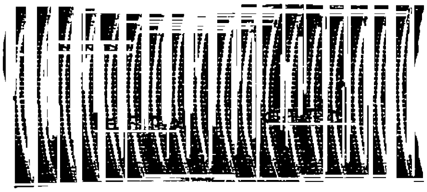
The voluntary or striated muscles form a large part of the body, and are known as the flesh or meat. Each muscle is embedded in a layer of connective tissue, and is made up of an aggregation of muscular fibres, which are united into bundles by means of areolar connective tissue. The individual fibres vary much in length, and may be as long as 4 or 5 cm. At each end of the muscle the fibres are firmly united to tough bundles of white fibres, which form the tendon of the muscle, and are attached as a rule to bones. Running in the connective tissue framework of the muscle we find a number of blood-vessels, capillaries, and nerves.

---

[1] The ciliary muscle furnishes an example of a muscle which, though unstriated, is under the control of the will.

On examination of a living muscle, each fibre is seen to consist of a series of alternate light and dark striæ, arranged at right angles to its long axis, and enclosed in a structureless sheath—the sarcolemma. Each band may be considered to be made up of a number of prisms (sarcomeres) side by side, with interstitial substance between them. The muscle prisms of adjacent discs are connected to form long columns (primitive fibrillæ, or sarcostyles). Each muscle prism is more transparent at the two ends than in the middle, thus giving rise to the appearance of light and dark striæ. In the middle of the light band is a line or row of dots (often appearing double), called Krause's membrane.

FIG 25



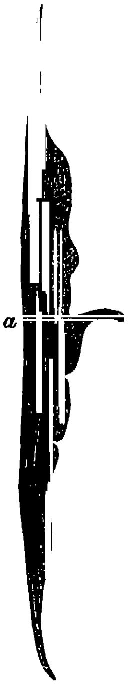
Muscular fibre of a mammal, examined fresh in serum, highly magnified (Schafer)

The development of this regular cross and longitudinal striation is closely connected with the evolution and specialisation of the muscular function, *i.e.* contraction. Contractility is among others a function of all undifferentiated protoplasm. Cells so constituted can only effect slow and weak contractions. Directly a specialisation of function is necessary and some cell or part of a cell has to contract rapidly in response to some stimulus from within or without, we find a differentiation both of form and of internal structure. In many cases.

s in the developing muscle of the embryo or the adult
uscles of many invertebrates, this differentiation affects only
art of the cell, so that while one part presents the ordinary

FIG 27

FIG 26



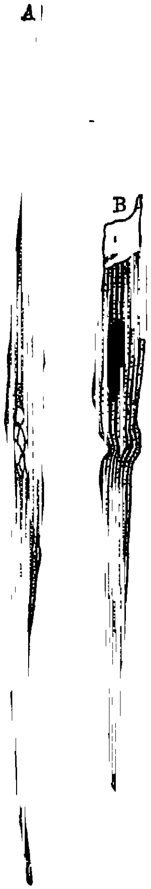


FIG 26 —Muscle-fibre of an ascaris *a* The differentiated contractile portion of the cell (After Hertwig)

FIG 27.—Muscle-fibres from the small intestine, showing the fine longitudinal striation (Schafer)

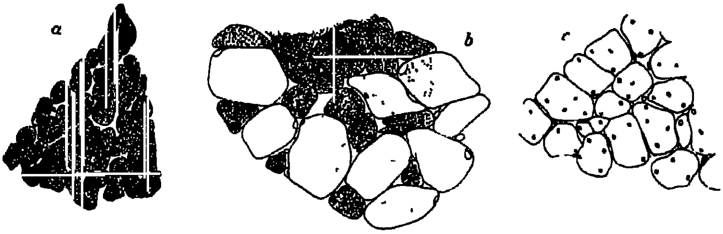
ranular appearance, the other half is finely and longitu-
inally striated, the striation being apparently due to the
evelopment of special contractile fibrillæ. In the slowly
ontracting unstriated muscle of the vertebrate intestine, the

longitudinal striation is with difficulty made out; but as the muscle rises in the scale of efficiency, the longitudinal striation becomes more apparent, and in the striated muscle of vertebrates, and still more in the wonderful wing-muscles of insects, which can perform three hundred complete contractions in a second, the longitudinal is associated with and often apparently subordinated to a transverse striation, due to the regular segmentation of the contractile fibrillæ or *sarcostyles*. Every muscular fibre, which presents any trace of histological differentiation, may be said to consist of contractile fibrillæ (sarcostyles), each composed of a series of contractile elements (*sarcous elements* or *sarcomeres*), and embedded in a granular material known as *sarcoplasm*. The enormous variation in the aspect of muscular fibres from different parts of the animal kingdom is largely conditioned by the varying relations, spatial and quantitative, of the sarcoplasm to the sarcostyles. Thus in the higher vertebrates, two types of voluntary muscular fibre are distinguished, according to the amount of sarcoplasm they contain: one rich in sarcoplasm, more granular in cross-section, and generally containing hæmoglobin; and the other poor in sarcoplasm, clear in cross-section, and containing no hæmoglobin. From the fact that the granular fibres are found chiefly in those muscles which have to carry out long-continued and powerful contractions, it seems reasonable to regard the interstitial sarcoplasm as the local food-supply of the active sarcostyles, although some authors have endowed the sarcoplasm with a contractile power of its own, differing only by its extremely prolonged character from the quick twitch of the sarcostyles. The connection between structure and activity of the muscle-fibres is well shown by Fig. 28.

In some animals, such as the rabbit, we find muscles consisting almost entirely of one or other of these varieties, but in most animals (amongst which we may reckon frog and man) the two varieties occur together in one muscle, so that what we have to say about the properties of voluntary muscle, which rests nearly entirely on experiments with frog's muscle, really has reference to a mixed muscle, *i e* muscle containing both red and white fibres

Since the sarcous element represents the contractile unit of the muscle, a knowledge of its intimate structure should be of great importance for the theory of muscular contraction. Unfortunately, however, we are here at the limits of the demonstrably visible. Where every worker has his own interpretation, it is only possible in this book to select one, which appears to be the most suggestive from the physiological standpoint. Schafer, working on the highly differentiated wing-muscle of the wasp, concludes that each sarcostyle is divided by Krause's membranes (the lines in the middle of each light stripe) into sarcomeres. Each sarcomere contains a darker substance near the centre divided into two parts by Hensen's disc. At each end of the sarcomere the contents are clear and hyaline. In the act of contraction, the clear material flows, according to Schafer, into tubular pores in the central dark material.

FIG. 28.



Transverse sections of the pectoral muscles of *a*, the falcon, *b*, the goose, and *c*, the domestic fowl. It will be noticed that the relative amount of granular or red fibres present varies directly as the bird's power of sustained flight. (After Knoll)

FIG. 29

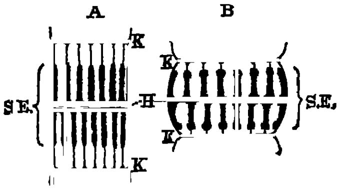
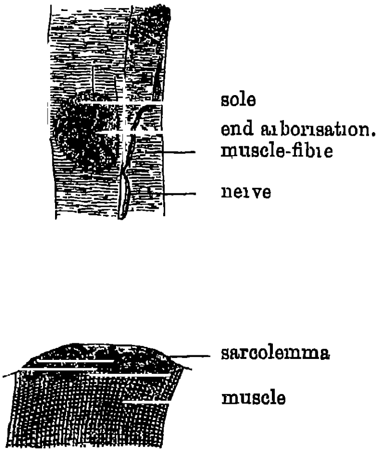


Diagram of a sarcomere in a moderately extended condition, A, and in a contracted condition, B, K, K, membranes of Krause, H, line or plane of Hensen, SE, poriferous sarcous element. (Schafer)

When a muscle-fibre, killed by osmic acid or alcohol, is examined under the microscope by polarised light, it is seen to be made up of alternate bands of singly and doubly refracting material. The doubly refracting (*anisotropous*) substance corresponds to the dark band, and the singly refracting (*isotropous*) to the light band. If however the living fibre be examined in the same way, it is found that nearly the whole of it is doubly refracting, the singly refracting substance appearing only as a meshwork with long parallel meshes corresponding to the muscle prisms. In short, in a living fibre the muscle prisms are anisotropous, the sarcoplasm isotropous.

When a muscle-fibre contracts, there is an apparent reversal of the situations of the light and dark stripes, owing to the fact that the interstitial sarcoplasm is squeezed out from between the bulging sarcomeres, and accumulates on each side of the membranes of Krause. The accumulation of sarcoplasm in this situation makes the previously light striæ appear dark, and the dark striæ by contrast lighter than they were before. That there is no true reversal of the striæ is shown by examining the muscle by polarised light, the two substances, isotropous and anisotropous, retaining their relative positions.

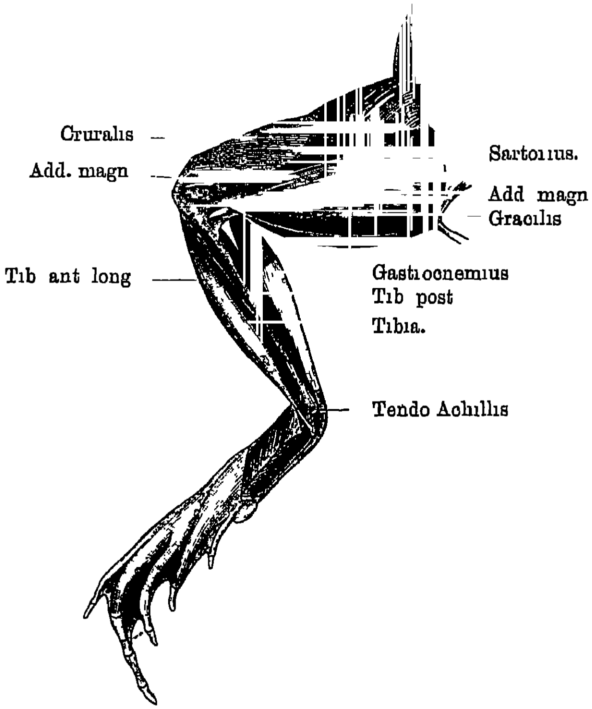
Fig 30



Motor end-plates of lizard

Every skeletal muscle is connected with the central nervous system by nerve-fibres, some conveying impressions from the muscle to the centre, the others acting as the path of the motor impulses from the centre to the muscle These latter—the motor nerves—end in the muscular fibre itself, by means of a special end-organ—the motor end-plate. The neurilemma of the nerve-fibre becomes continuous with the sarcolemma, the medullary sheath ends suddenly, while the axis cylinder ramifies in a mass of undifferentiated protoplasm, containing nuclei, and lying in contact with the contractile substance of the muscle immediately under the sarcolemma.

Fig 31



Muscles of hinder extremity of frog (after Ecker)

So far as we can tell at present, the ultimate ramifications of the axis-cylinder end freely and do not enter into organic connection with the contractile substance itself.

Most of our knowledge on the subject of muscle has been derived from the study of the gastrocnemius and sartorius muscles of the frog. The position of these muscles is shown in the accompanying diagram (Fig. 31). The gastrocnemius which, with the attached sciatic nerve, is most frequently employed as a nerve-muscle preparation, forms a thick belly immediately under the skin at the back of the leg, and arises by two tendons from the lower end of the femur and the outer side of the knee-joint. The two tendons converge towards the centre of the muscle, uniting about its middle, and from them a number of short muscular fibres arise, passing backwards and dorsally to be inserted into a flat aponeurosis covering the lower half of the muscle, which ends in the tendo Achillis. On account of this irregular arrangement of the muscular fibres, the gastrocnemius can only be employed when the contraction of the muscle as a whole is the object of investigation. The effective cross-area of the fibres is much greater than the actual cross-section of the muscle, so that, while the actual shortening of the gastrocnemius is but small, its strength of contraction is considerable.

The sartorius muscle consists of a thin band of muscle-fibres running parallel from one end of the muscle to the other. It lies on the ventral surface of the thigh, arising from the symphysis pubis by a thin flat tendon, and is inserted by a narrow tendon into the inner side of the head of the tibia. On account of the regularity with which its fibres are disposed, this muscle is of especial value in experiments on the local conditions of a muscle-fibre accompanying its activity. When a greater mass of approximately parallel fibres is necessary, recourse may be had to a preparation consisting of the gracilis and semi-membranosus muscles together. This latter muscle lies dorsally to the gracilis muscle which is shown in the illustration.

SECTION 2

EXCITATION OF MUSCLE

A muscle may be caused to contract in various ways. Normally it contracts only in response to impulses starting in the central nervous system and transmitted down the nerves. But contraction may be artificially excited in various ways in a muscle removed from the body. If we make a muscle-nerve preparation (*i.e.* a muscle with as long a piece of its nerve as possible attached to it), such as the gastrocnemius of the frog with the sciatic nerve, we find we can cause contraction by various forms of stimuli—mechanical, thermal, or electrical—applied to the muscle or the nerve (direct and indirect stimulation). Thus the muscle responds with a twitch if we pass an induction shock through it or its nerve, or pinch either with a pair of forceps. Or we may use chemical stimuli, and cause contraction by the application of strong glycerin or salt solution to the nerve.

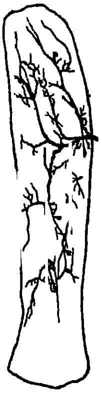
These experiments do not prove conclusively that muscle itself is irritable. It might be urged that, when we pinched or burnt the muscle, we stimulated, not the muscle substance itself, but the terminal ramifications of the nerve in the muscle, and that these in their turn incited the muscle to contract. But the independent excitability of muscle is shown clearly by the following experiment.

A frog, whose brain has been previously destroyed, is pinned on a board, and the sciatic nerves on each side exposed. A ligature is then passed round the right thigh underneath the nerve, and tied tightly so as to close effectually all the blood-vessels supplying the limbs, without interfering with the blood-supply to the nerve. Two drops of a 1 per cent. solution of curare are then injected into the dorsal lymph-sac. After the lapse of a quarter of an hour it is found that the strongest stimuli may be applied to the left sciatic nerve without causing any contraction of the muscles it supplies. On the right side however, stimulation of the nerve is as efficacious as before. Both gastrocnemii respond readily to direct stimulation, showing that the muscles are not affected by the drug. Since both sciatic nerves have been exposed to the influence of the curare, it is evident that the difference on the two sides cannot be due to any deleterious effect on them by the curare. We have also excluded the muscles themselves, so we must conclude that the curare paralyses the muscles by affecting the terminations of the nerve within the muscle, and probably the end-plates themselves.

This experiment therefore teaches us that muscle can be excited to contract by direct stimulation, even when the terminal ramifications of the nerve within it are paralysed, so that stimulation of them would be without effect.

The same fact may be demonstrated in a different way by means of chemical stimuli. It is found that whereas strong glycerin excites nerve-fibres, it is without effect on muscle-fibres; while on the other hand weak ammonia is a strong excitant for muscle, but is without effect on nerve. Thus if the frog's sartorius be dissected out and the lower end dipped in glycerin, no effect is produced. On snipping off the lower third of the muscle and then immersing the cut end in glycerin, a twitch at once occurs. The lower end contains no nerve-fibres (Fig. 32), and it is only when a section containing nerve-fibres is exposed to the action of glycerin that con-

Fig 32



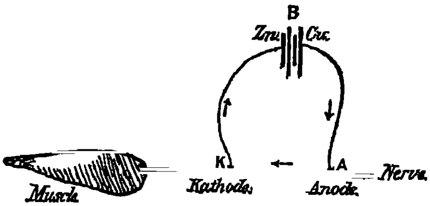
The ramification of the nerve-fibres within the sartorius muscle of the frog, showing the freedom of the lower portion of the muscle from nerve-fibres (Kuhne) traction takes place. On the other hand, mere exposure of muscle to the vapour of dilute ammonia causes contraction (and subsequent death), although the nerve to the muscle can be immersed in the solution without any excitation being produced.

Of all the different stimuli that we have mentioned as capable of exciting muscular contraction, the electrical is that most frequently employed. It is easy, using this form, to graduate accurately the intensity and duration of the stimulus. At the same time the stimulus may be applied many times to any point on the muscle or nerve without killing the part stimulated, whereas with other forms of stimulus it is difficult to obtain excitatory effects without injuring to a greater or less extent the part stimulated.

Two forms of electrical stimuli are employed,—the make and break of a constant current, and the induction currents of high intensity and short duration obtained from an induction coil.

Constant current.—As a source of constant current a Daniell's cell is generally employed (*vide* Appendix). In this cell the copper is the negative and the zinc the positive *element*. The current therefore passes in the cell from zinc to copper, and outside the cell from copper to zinc. If therefore wires be attached to the zinc and copper, the wire attached to the former will be the negative, and that to the latter the positive *pole*. If we connect such wires with the nerve or muscle of a nerve-muscle preparation (as in Fig. 33), the current will flow from copper to the nerve at A, and along the nerve from A to K. At K the current will leave the nerve to flow to the zinc of the battery, so completing the circuit. The point at which the current enters the nerve (*i.e.* the point of the nerve connected with the positive *pole*

FIG 33

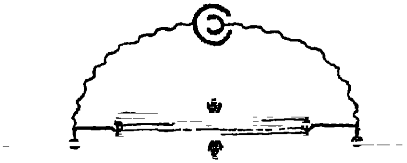


of the battery) is called the *anode*, and the point at which the current leaves the nerve is called the *kathode*. The wires by which the current is conducted to and from the nerve are called the *electrodes*.

If a weak current from a Daniell's cell (or any other form of battery) be passed through a muscle or any part of its nerve, we find that at the make of the current the muscle gives a single sharp contraction—a *muscle-twitch*. No effect is produced during the passage of the current or when it is broken, the muscle remaining perfectly quiescent.[1] If the current is now increased we find that the muscle responds to both make and break, remaining however quiescent during the passage of the current. Using a current of moderate strength, we find the contraction due to make is more energetic than that due to break.

Thus stimulation is caused by the make and break of a constant current, the make stimulus being more effective than the break. Besides this difference in intensity, there is a difference in the point from which excitation starts. *A make contraction starts from the kathode, a break contraction from the anode.* This is well shown by the two following experiments.

FIG. 34.



Sartorius clamped in middle and attached to levers at either end.

a. A curarised sartorius muscle of the frog (Fig. 34), with its bony insertions still attached, is fastened at the two ends to two electrodes, which are able to swing when the muscle contracts, and are attached by threads to levers which serve to record the contraction. The middle of the muscle is then fixed by clamping it lightly. A circuit is arranged so that a constant current can be sent through the electrodes and the whole length of the muscle. It is found, on making the current, that the lever attached to the kathode—that is, to the electrode by which the current leaves the muscle—rises before the other lever. On the other hand, on breaking the current, the lever at the anode rises first, showing that the anodic half of the muscle contracts before the kathodic half.

---

[1] This statement is not absolutely correct No propagated contraction, as a rule, is produced *during* the passage of a constant current Careful observation will show however that there is a state of continued contraction limited to the immediate neighbourhood of the kathode, which lasts as long as the current is passed through the muscle.

b. The irritability of a muscle, *i.e.* its power of responding to a stimulus by contracting, is intimately dependent on the life of the muscle. If the muscle be injured or killed at any spot, its irritability at this spot will be therefore diminished or destroyed. Hence, if we stimulate a muscle at the injured spot, no contraction will ensue. This fact may be used to demonstrate the production of excitation at kathode on make, and at anode on break of a constant current.

FIG. 35.

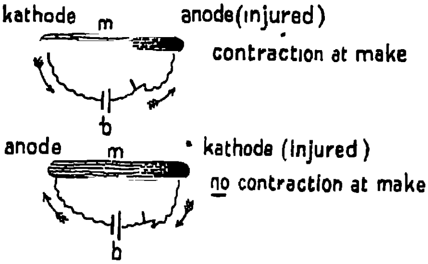


Diagram to show the effect of local injury on the excitability of a muscle *b*, battery, *m*, muscle The arrows indicate the direction of the current

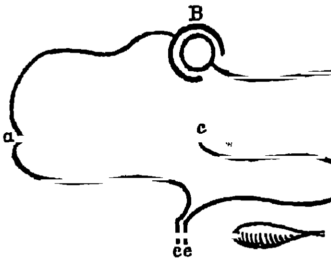
A muscle with parallel fibres, such as the sartorius, is injured at one end, and a constant current passed, first from the injured to the uninjured end, and then in the reverse direction. It is found in the former case, when the anode is on the injured part (which is therefore less excitable), that break of the current is ineffective, and in the latter, when the kathode is on the injured surface, that the make stimulus is ineffective, showing that the part excited corresponds to the kathode at make and to the anode at break.

Induced currents.—In using these the muscle or nerve is stimulated by the current of momentary duration produced in the secondary circuit of an induction coil by the make or break of a constant current in the primary. The strength of the shock is graduated by moving the secondary nearer to or farther away from the primary coil.

Using this mode of stimulus, it is found that the contraction on break of the constant current is much stronger than that on make. It must not be imagined however that there is any contradiction between this and the fact that the make of a constant current is a stronger stimulus than the break.

When we put a muscle in the secondary circuit and make a current in the primary, there is a current of momentary duration induced in the secondary; so that there is a current *made and broken* through the muscle, and the same thing takes place again when the primary circuit is broken. It has been shown that, when we use currents of such short duration, the break stimulus is ineffective; so in both cases, whether we make or break the current in the primary circuit, we are dealing with a *make* stimulus in the muscle. The difference in the efficacy of make and break induction shocks is purely physical, and depends on the fact that the current induced in the secondary coil on make is of slower rise and smaller potential than that produced at break. (See Appendix.)

FIG. 36



We see therefore that the efficiency of an electrical stimulus depends on the rate of variation of the current employed, and within wide limits is proportional to this rate. If, instead of suddenly diminishing and increasing the current passing through an irritable structure, we carry out the change gradually, no excitatory effect is produced, even although the current may finally attain a considerable strength. This fact may be demonstrated with the help of the rheocord (Fig. 36), which consists of a simple wire *ab* through which a current is led. Two wires pass from *a* and a movable rider *c* to the nerve or muscle. It is evident that if *c* be in close proximity to *a*, no current will flow through the muscle. But as *c* is pushed towards *b*, the current through the nerve gradually increases. It will be found that if the rider be moved slowly from *a* to *b*, or in the reverse direction, no effect is produced, whereas a quick movement in either direction causes excitation. We may say therefore that the excitatory effect of a current increases with—

1. The intensity of the current.
2. The rate of change of the current.
3. (In the case of nerve) The length of nerve through which the current passes.

The second of these conditions needs however some correction. As we increase the rate of change of current, by employing in the case of induced currents more and more rapid alternations, we find that the excitatory effect, instead of increasing, begins to diminish and finally disappears, so that high frequency currents of enormous tension can, as in Tesla's experiments, be led through the body without any apparent physiological effect. On the other hand, by using more sluggish forms of irritable tissue, we may find that even our induction shocks are too rapid for effective excitation. Thus the red muscles of the slow-moving tortoise react better to the slow make than to the sudden break induction shock, and many forms of unstriated muscle are unaffected by either make or break shock. We must conclude therefore that for each tissue there is an optimum rate of change varying with the character of the tissue, at which the energy necessary to produce a response is at a minimum. This optimum rate of change is spoken of by Waller as the 'characteristic' of an irritable tissue, and has been determined by him for nerve.

A *minimal* stimulus is the weakest stimulus that will produce a contraction A *maximal* stimulus is one that produces the strongest contraction a muscle is capable of under the effects of a single stimulus A *submaximal* stimulus is any strength of stimulus between these two extremes.

SECTION 3

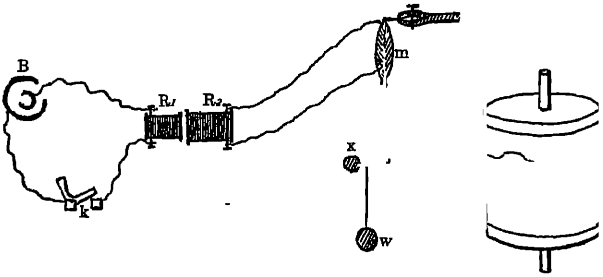
THE MECHANICAL CHANGES THAT A MUSCLE UNDERGOES WHEN IT CONTRACTS

Change of Form

The most evident change about a muscle when it contracts is of form. It becomes shorter and thicker, its bulk remaining unaltered.

To study this change more closely, it is necessary to obtain a graphic record of the contraction. For this purpose the femur, to which the gastrocnemius of the muscle-nerve preparation is attached, is clamped firmly, and the tendo Achillis attached by a thread to a light lever, free to move round an axis at one end. The point of this lever is armed with a bristle (anything that is stiff and pointed will do), which just touches the blackened surface of a piece of glazed paper. This paper is stretched round a cylinder (drum) which can be made to rotate at any constant speed required. If the drum is moving, the point of the bristle draws a horizontal white line on the smoked paper.

FIG. 37



Arrangement of apparatus for recording simple muscle twitch

If however a single induction shock be sent through the nerve of the preparation, the lever is jerked up, falling again almost directly, and a curve is drawn like that shown in Fig. 38.

A similar curve is obtained if the muscle be stimulated directly.

In all such graphic records we should have also—

1. *A time record.*—This is furnished by means of a small electro-magnet, armed with a pointed lever writing on the smoked surface. This electro-magnet (time marker or signal) is made to vibrate 100 times a second (more or less as may be required) by putting it in a circuit which is made and broken 100 times a second by means of a tuning-fork vibrating at that rate. The tuning-fork is maintained in vibration in the same way as the Wagner's hammer of an induction coil.

2. *A record of the exact point at which the nerve or muscle is stimulated.*—This may be obtained in two ways:

a. When using the pendulum or trigger myograph, in both of which the recording surface is a smoked flat surface on a glass plate, this latter is so arranged that it knocks over a key as it shoots across, and so breaks the primary circuit and excites the nerve or muscle of the preparation. As we know the exact point that the plate reaches when it knocks over the key, we can mark on the contraction curve the exact moment at which stimulation took place.

FIG. 38.

Curve of single muscle-twitch taken on a rapidly moving surface (pendulum myograph) (from Yeo).

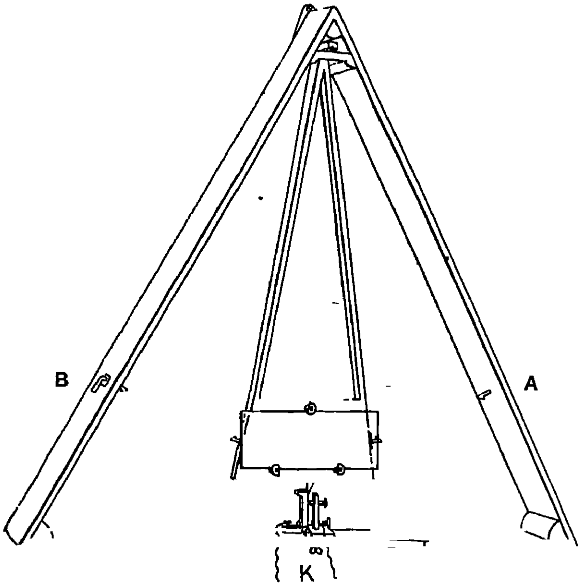
b. If we wish to make and break the primary circuit at will by means of a key, a small electro-magnetic signal, interposed in the circuit, is arranged to write on the revolving drum, and so mark the point of stimulation.

In the figure (Fig. 38) the upper line is the curve drawn by the lever of the muscle as it contracts; the small upright line shows the point at which the muscle was stimulated;

and the second line is the tracing of the chronograph, every vibration representing $\frac{1}{444}$ of a second.

In the pendulum myograph (Fig. 39) a smoked glass plate is carried on a heavy iron pendulum. At each side the pendulum is armed with a catch, which fits on to other catches at the side of the triangular box, from the apex on which the pendulum is suspended. At its lower part the pendulum carries a projecting piece which can knock over the 'kick-over' key (K), thus breaking a circuit in which is included the primary coil of an induction coil. The lever attached to the muscle is arranged so as to write lightly on the glass plate, Everything being ready, and the key (K) closed, the pendulum is raised to A, the catch (A) is then released, and the pendulum falls at an ever-accelerating rate and then rises again, gradually slowing off until it is caught again at B. As it passes by the key it breaks the circuit. A break induction shock is sent into the muscle or nerve, which contracts, and a curve is obtained similar to that shown in Fig. 38. Since the rate of the pendulum is constantly varying throughout its course, it is necessary to have a tuning-fork, or time-marker actuated electrically by a tuning-fork, writing just below the muscle-lever.

FIG. 39.



Simple form of pendulum myograph

In the spring myograph, otherwise known as the trigger or shooter myograph (Fig. 40), a smoked glass plate is also used. 'The frame supporting the glass plate slides on two horizontal steel wires. To make the instrument ready for use, the frame is moved to one side, which compresses a short spring. When the catch holding it in this position is released by the trigger, the spring which only acts for a short space, gives the frame and the glass plate a rapid horizontal motion; and the momentum carries the glass plate through the rest of the distance, till stopped by the buffers The velocity during this time is nearly constant, as the friction of the guides is small. Two keys are knocked over by pins on the frame and break electric circuits. The relative positions at which the circuits are broken can be altered by a convenient adjustment A tuning-fork vibrating about 100 per second fixed to the base of the instrument marks the time; its prongs are sprung apart by a block between their ends, and the same action which releases the glass plate also frees the fork by removing the block and allows it to vibrate; a writing style then draws a sinuous line on the smoked surface of the moving glass plate. A muscle lever with a scale-pan attached also forms part of the instrument.'[1]

Fig. 40.

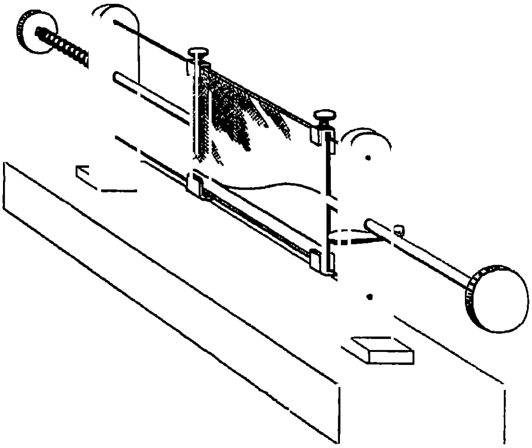


Diagram of spring myograph, or 'shooter'

It will be seen that a simple muscular contraction or twitch, such as we have in Fig. 38, produced by a momentary stimulus, consists of three main phases :

1. A phase during which no apparent change takes place in the muscle, or at any rate none which gives rise to any movement of the lever. This is called the *latent period.*

2. A phase of shortening, or contraction.

3. A phase of relaxation, or return to the original length.

The small curves seen after the main curve are due to elastic vibrations of the lever, and do not indicate any changes occurring in the muscle itself. From the time-marking below the tracing, we see that the latent period occupies about

---

[1] From Catalogue of Camb Sci Inst Co

$\frac{1}{100}$ of a second, the phase of shortening $\frac{4}{100}$, and the relaxation $\frac{5}{100}$ second.

Thus a single muscle-twitch is completed in about $\frac{1}{10}$ of a second. It must be remembered however that this number is only approximate, and varies with the temperature of the muscle and its condition, being much longer in a fatigued muscle.

It is generally said that, during the latent period, invisible preparatory changes are taking place in the muscle, and these changes are supposed to be indicated by the electrical change accompanying a muscular contraction, which is generally described as taking place during the latent period. But recent experiments have tended more and more to shorten the latent period, and it now seems probable that nearly the whole of the latent period is due partly to instrumental inertia, and partly to the mechanical inertia of the muscle itself. For living muscle is elastic and very extensible, and the effect of contraction of any given part of it will be first to stretch the adjacent part, and afterwards to move the part of the muscle to which the lever is attached.[1]

Sanderson and Burch have measured the mechanical latency of muscle by a photographic method. The thickening of the muscle at the point stimulated was recorded graphically by photographing the outline of the muscle on a slit, behind which was a moving sensitive plate. Thus avoiding all instrumental inertia, and diminishing the inertia of the muscle to a minimum, the mechanical latent period was found to be only 0·0025 second. The electrical change, however, began at the moment of stimulation, and had reached its culminating point when the mechanical change was commencing.

As we should expect from the preceding paragraph, the latent period is much increased by increasing the load. It is also lengthened by cold and fatigue. It is longer in the red than in the white muscles.

---

[1] The effect of the extensibility of muscle in lengthening the latent period will perhaps be more intelligible if illustrated by an example If we have a weight supported by a rigid wire, and suddenly pull the upper end of the wire so as to raise the weight, the latter will rise instantaneously. If however the weight be suspended by a piece of elastic, it will not follow the pull exactly, but will lag behind, the first part of the pull being occupied with stretching the indiarubber, and only when this is stretched to a certain degree will the weight begin to rise The same retardation of the pull would be observed if, instead of indiarubber, we used a piece of living muscle

The *height* of the contraction depends—

1. On the strength of the stimulus.

2. On the load; the height being smaller, the greater the weight the muscle has to raise. If the load is gradually increased, a point is reached when the muscle can no longer raise it. This weight represents the 'absolute force' of the muscle. In determining it the muscle is 'after-loaded,' that is to say, the lever is supported by a screw in its unweighted position, so that the weight cannot act on the muscle till the latter begins to contract. In human muscle the absolute force has been found to amount to 6,000 to 8,000 grams per square centimetre of cross area of the muscle.

The relaxation of muscle is helped by a moderate load, and in a normal condition is complete. It is not active—that is to say, is not due to a contraction in the transverse direction—but is a passive effect of extension and elastic rebound. This may be shown by allowing a muscle to contract while floating on mercury. The subsequent lengthening on relaxation is very incomplete.

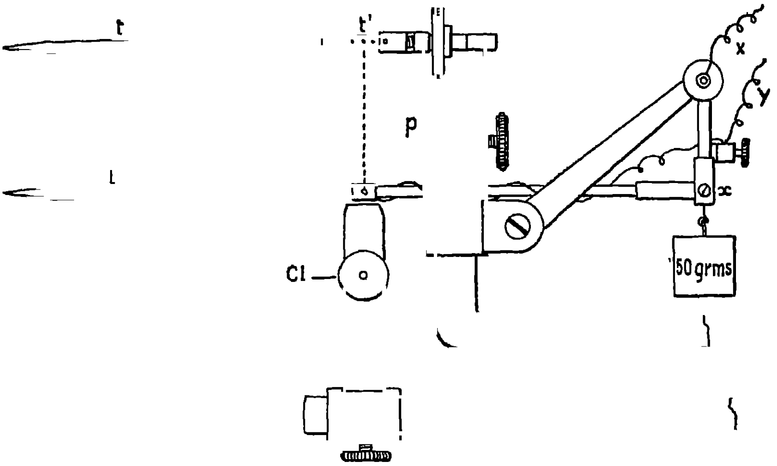
Isotonic and Isometric Contractions

In order to obtain a true curve of a muscle-twitch special precautions are necessary to avoid the effects of instrumental inertia. When the muscle begins to contract it imparts a very rapid movement to the lever, which therefore tends to overshoot the mark and deform the curve. This source of error may be almost avoided by making the lever as light as possible, and hanging the extending weight in close proximity to the axle of the lever, as shown in Fig 41. Since the energy of a moving mass is proportional to the square of the velocity $\left(=\frac{mv^2}{2}\right)$, and the tension due to the weight as well as the velocity on contraction is directly proportional to the distance of the weight from the axis, it follows that it is better to load the muscle with 40 grams 1 millimetre from the axis than with 1 gram 40 millimetres from the axis, though the tension put on the muscle will be the same in both cases.

In the first case the energy of the moving mass will be proportional to $\frac{40 \times (1)^2}{2} = 20$, and in the second to $\frac{1 \times (40)^2}{2} = 800$, and it is this energy which determines the overshooting of the lever and the deformation of the curve. Since throughout the contraction the lever follows the muscle in its movement, the tension on the muscle remains the same throughout, and the method is therefore known as the *isotonic method*

In many cases it is of importance to be able to record the development of the energy (*i.e.* the tension) of the active muscle apart from any changes in its length. For this purpose the muscle is allowed to contract against a strong spring, the movements of which are magnified by means of a very long lever. Thus the shortening of the muscle is almost entirely prevented, but the increase in its tension causes a minute but proportionate movement of the spring, which is recorded by means of the lever. Since in this case the length or measurement of the muscle remains approximately constant, while the tension is continually varying throughout the contraction, it is known as the *isometric method*. The great magnification necessary in this method introduces serious sources of error, but it seems that, if all due precautions be taken to avoid these errors, the isometric curve differs very little in form from the isotonic, displaying only a somewhat quicker development of energy at the beginning of contraction.

FIG. 41.



Blix apparatus for recording isometric and isotonic curves synchronically (Miss Buchanan). *p*, the steel cylindrical support with jointed steel arm to bear the isotonic lever *l*, which consists of a strip of bamboo with an aluminium tip *t*, the isometric lever, also of bamboo, except for a short metal part *t'* in which are holes for fixing the muscle. The two wires from an induction coil are brought, one to ×, which is in connection with the support and hence with the metal bar *t'*, the other to *y*, which is insulated from the support but connected by a copper wire with a thin piece of copper surrounding the isotonic lever at the point where the muscle is attached to it. *Cl*, clamp for fixing the lower end of the muscle when an isometric curve is to be taken. The axis of the isotonic lever is at *x*, close to which is hung the weight of 50 grms.

Propagation of Contraction. The Contraction Wave

The whole muscle does not as a rule contract simultaneously. When excited from its nerve the contraction begins at the end-plates and spreads in both directions through the muscle. The rate of propagation of the contraction wave can only be measured by employing a curarised muscle, so as to avoid the wide spreading of the excitatory change by means of the intra-muscular nerve-endings. For this purpose a curarised sartorius muscle is taken, stimulated at one end, and the thickening of the muscle recorded by means of two levers placed, one near the exciting electrodes and the second at the other end of the muscle, as shown in the diagram (Fig. 42). The difference between the latent periods of the two curves represents the time taken by the contraction wave in travelling from *a* to *b*. By measurements carried out in this way it is found that the rate of propagation of the contraction in frog's muscle is 3 to 4 metres per second; in the muscle of warm-blooded animals it may amount to 6 metres.

FIG. 42.

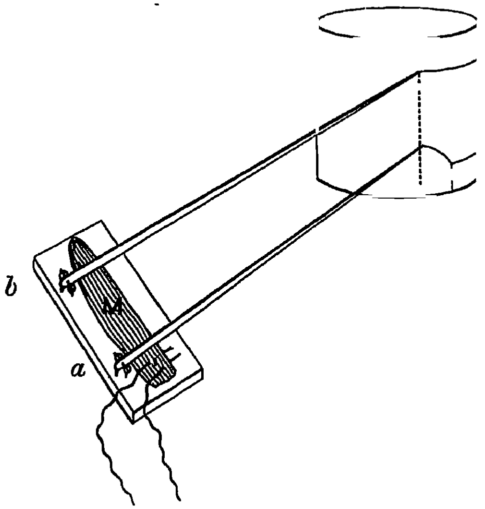


Diagram of arrangement for recording the contraction wave in a curarised sartorius.

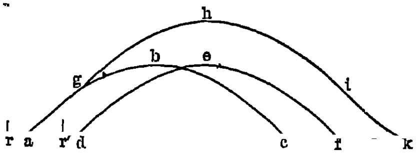
The actual duration of the contraction at any given point is necessarily smaller than that of the whole muscle, and amounts in frog's muscle to only 0·05-0·09 second, about half the duration of the contraction of a whole muscle of moderate length. The *length of the wave* is obtained by multiplying the rate of transmission by the duration of the wave at any one point. It varies therefore in frog's muscle between 3,000 × ·05 (=150) and 4,000 × ·09 (= 360) millimetres. Thus the muscle-fibres in the frog are much too short to accommodate the whole length of the wave, and the contraction of the whole muscle must be made up of the summated effects of the contraction wave as it passes from point to point. Hence the longer the muscle, the more must the contraction be lengthened by the time taken up in propagation from one end to another.

Summation of Contractions

If a muscle is stimulated twice in succession, so that the second stimulus follows the first before the muscle has reached its maximum shortening, we get a combination of the effects of the two, which results in a stronger contraction. The second stimulus has the same effect on the muscle as if the condition of contraction, which this latter has attained when the stimulus reaches it, were its normal length.

Thus, if the period that elapses between the two stimuli is equal to the duration of the first part of the contraction (from its beginning to the maximum height), the shortening of the muscle may be doubled. Fig. 43 shows the effect of two successive stimuli at an interval of about $\frac{1}{20}$ second. The two lower curves represent the contractions which would have resulted from either of the stimuli alone.

FIG. 43.



Muscle curves showing summation of stimuli. r and r′, the points at which the stimuli were sent into the nerve. From the first stimulus alone the curve a b c would be obtained. From r′ the curve d e f is obtained These two curves are *summated* to form the curve a g h i k when both stimuli are sent in at the interval rr′

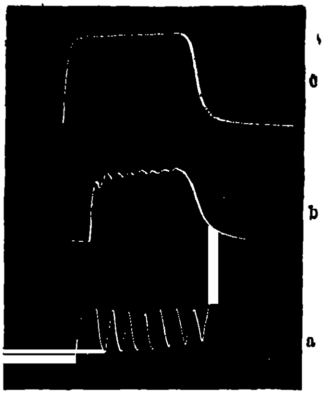
This piling up of one contraction on the other is spoken of as *summation.*

Tetanus

If a muscle be stimulated so many times in a second (*e.g.* with the interrupted current of an ordinary induction coil) that it has no time to relax between one stimulus and another, we get a prolonged steady contraction, which is much stronger than the maximal muscle-twitch, owing to the summation of the rapidly following stimuli. This condition is called *tetanus.*

The rapidity of stimulation needed to produce an unbroken tetanus depends on the duration of a single muscle-twitch, and varies therefore according to the kind and condition of the muscle. Thus the rapidity need only be small in the case of cooled and tired muscles, or of the red muscles of the rabbit and tortoise. The rate varies from about 15 in the case of red muscles to 30 or 40 for white muscles. For the much more highly differentiated muscles of insects the rate is probably very much greater.

FIG. 44.



Curves showing formation of tetanus (from frog's gastrocnemius) a. Six stimuli per sec. b. Ten stimuli per sec. c. Thirty stimuli per sec

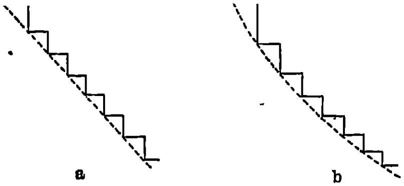
Extensibility

Besides the change of form, we find changes in the elasticity and extensibility of muscle taking place during contraction.

Living muscle in a perfectly normal condition is distinguished by its slight but perfect elasticity; that is to say, it is considerably stretched by a slight force (in the longitudinal direction), but returns to its original length when the extending weight is removed. The length to which muscle is stretched is not proportional to the weight used, but any given increment of weight gives rise to less elongation, the more the muscle is already stretched. The accompanying curves show the elongation of muscle as compared with a piece of indiarubber, when the weight on it is uniformly increased.

Dead muscle is less extensible and its elasticity is less perfect. A given weight applied to a dead muscle will not stretch it so much as when the muscle was alive; but the dead muscle does not return to its original length when the weight is removed.

Fig 45.



Extensibility of indiarubber (a) compared with that of a frog's gastrocnemius muscle (b)

A contracted muscle on the other hand is more extensible than a muscle at rest. A gram applied to a tetanised gastrocnemius will cause greater lengthening than if it were applied to the same muscle at rest. At the same time the elasticity is more perfect—that is to say, when the weight is removed, the muscle returns more quickly to its original length.

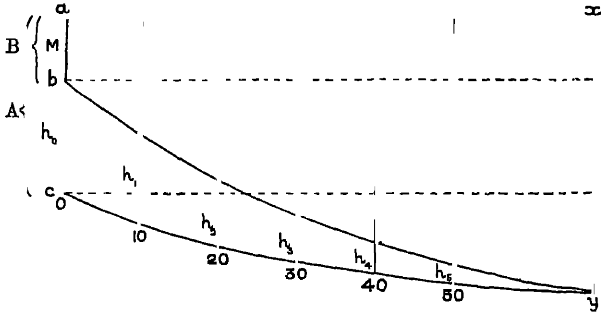
SECTION 4

THE PRODUCTION OF WORK AND HEAT BY VOLUNTARY MUSCLE

THE EXTERNAL WORK DONE BY A MUSCLE

We have already seen that the height of contraction of a muscle diminishes as the load is increased. This diminution in height is at first very slight and is not proportional to the load, so that the work done by the muscle, which is measured by the product of the weight lifted and the height to which it is raised, $w \times h$, with increase of weight rises at first quickly then more slowly to a maximum, and then, on further increasing the load, sinks.

FIG 46



Curve showing the length of a muscle under various loads in the contracted condition B, and uncontracted condition A The double lines *a b* etc represent the contracted muscle, while the long single lines *a c* etc show the length of the inactive muscle

This will be rendered clearer by reference to the diagram (Fig. 46) representing the lengths of the resting and contracted muscle with various loads. The lines h_0, h_1, etc., are the actual height of contraction of the muscle when loaded with weights of 0, 10, 20 grams, etc. The work in each case is given by $h_0 \times 0$, $h_1 \times 10$, $h_2 \times 20$, $h_3 \times 30$, etc. By inspection it will be seen that—

$$0.h_0 < 10.h_1 < 20.h_2 < 30.h_3 > 40.h_4 > 50.h_5.$$

In this case therefore the maximum of mechanical work is obtained when the muscle is loaded with about 30 grams. This increase of work with increased load shows that the amount of external work performed by a muscle is not a constant quantity, nor one determined solely by the strength of stimulus, but is essentially conditioned by the tension under which the muscle contracts. The muscle is in fact endowed with a certain power of adaptation, so that it can respond with increased efforts or expenditure of energy when it has more work set it to do. It might be thought that the increased mechanical energy evolved under these conditions had its origin at the expense of some other form of energy, such as heat or electrical changes, but it is found that increased tension augments all the processes of muscle, including chemical changes and the production of heat. This excitatory effect of tension on skeletal muscle is aided in all the higher animals by impulses which pass through the central nervous system, the nature of which we shall have to discuss later on when dealing with the question of so-called 'tendon reflexes.' The phenomenon however is common to all forms of contractile tissues, and is indeed much better marked in such forms as the heart-muscle and the unstriated muscular fibres of the viscera. One may occasionally find that the application of a slight load to a skeletal muscle actually increases the height of the contraction, especially if the muscle be not after-loaded. In the heart-muscle an increase of tension within physiological limits causes invariably increased contraction—a fact of very great importance for the physiology of compensation in heart disease. This excitatory influence affects not only the strength of contraction but also the automatic, rhythmic, and conducting power of the muscle ; and in some cases, as in the snail's heart, the rate of beat is absolutely determined by the tension, the heart stopping altogether if the tension be reduced to nothing.

The Production of Heat

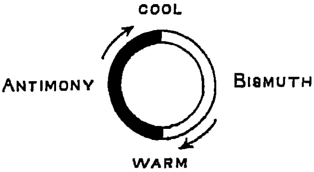
The experience of everyday life teaches us that muscular exercise is associated with increased production of heat. A man walks fast on a frosty day to keep himself warm ; and we find this observation confirmed when we investigate the contraction of an isolated muscle outside the body.

Thus, if a frog's muscle is tetanised, its temperature rises from 0·14° to 0·18° C., and for each single twitch from 0·001° to 0·005° C

It is evident that such small changes in temperature as 0·001° cannot be estimated by ordinary thermometric methods. For this purpose a thermopile must be used.

The construction of a thermopile depends on the fact that, when the junctions of a circuit made of two metals are at different temperatures, a current of electricity generally flows through the circuit This current can be measured by means of a galvanometer, and is proportional to the difference of temperature between the two junctions. Thus in the circuit (Fig 47) composed of two metals, antimony and bismuth, if the upper junction be cooled, there will be a current flowing from antimony to bismuth in the direction of the arrow, and this current will within limits be proportional to the difference of temperature

FIG 47.



To measure the production of heat during muscular contraction, a small flat thermopile (containing four or six elements composed of iron and German silver) is fixed with one of its ends between two frog's gastrocnemii Another exactly similar pile, but reversed, is placed between two other gastrocnemii, which are kept resting and at a perfectly constant temperature The arrangement of the piles is shown in the diagram (Fig. 48) So long as the two piles are at the same temperature no current flows, but, with a sensitive galvanometer, the slightest difference of temperature, such as that caused by the contraction of one pair of muscles, at once causes a deflection of the galvanometer, the extent and direction of which enable us to estimate exactly the seat and amount of heat produced

Another method of measuring the heat production in muscle takes advantage of the fact that the electrical resistance of a wire increases with a rise of temperature In both methods we convert heat into electrical changes, since our means of judging of electrical differences are more sensitive than is the case with any other physical change.

In large animals the production of heat in muscular contraction can be easily shown by inserting the bulb of a thermometer between the thigh muscles, and stimulating the spinal cord. The rise of temperature produced in this way may amount to several degrees.

The discovery of exact means of measuring the heat production during contraction was naturally utilised to determine the relation between the heat produced and the work done under varying conditions. In the muscle as in a steam engine, we have a conversion of potential energy stored up in carbon compounds into kinetic energy, which may appear as work and heat. In the engine there is a definite ratio between work and heat. Only a certain small proportion of the total energy can be utilised as work, the rest being dissipated as heat. The exact proportion depends on the difference of temperatures that is available in the machine, and in the best engines at our disposal amounts to one-tenth. If the machine does no work, the heat production is increased by the amount corresponding to the work. The same is true to a certain extent in muscle. If a muscle be allowed to contract and relax twenty times when loaded by a weight, the total external work done will be nothing. If however the weight be attached to the axle of a wheel, which is provided with a catch so that the weight can only be drawn up (Fig. 49), and the muscle be allowed to pull at each contraction on the circumference of the wheel, at each contraction work is done. It is found that in the latter case the muscle is less heated than in the former, and the difference is equivalent to the work done in raising the weight. But as soon as we begin to alter the work by altering the weight, we are at once met by the difficulty that increased tension augments all the properties of the muscle,

FIG 48

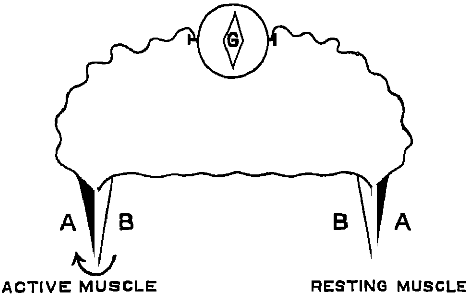


Diagram of the arrangement for showing the development of heat during muscular contraction A B, B A, two thermo-electric junctions; G, galvanometer. (After Waller) and with the same stimulus both work and heat production are raised by increasing the load. In fact the maximum amount of heat is produced when the muscle is made to contract against a strong spring, so that it cannot shorten at all (isometric contraction).

In view of the comparison of the muscle to a heat engine, it becomes interesting to inquire into its efficiency, *i.e.* the relation of the work to the total energy expended. This amount is found to vary within very wide limits. In a fresh muscle the heat energy may be twenty-five times as great as the work energy, but the heat evolved with each contraction diminishes with fatigue more rapidly than the work done, so that the proportion may fall to as low as three to one. In

FIG 49

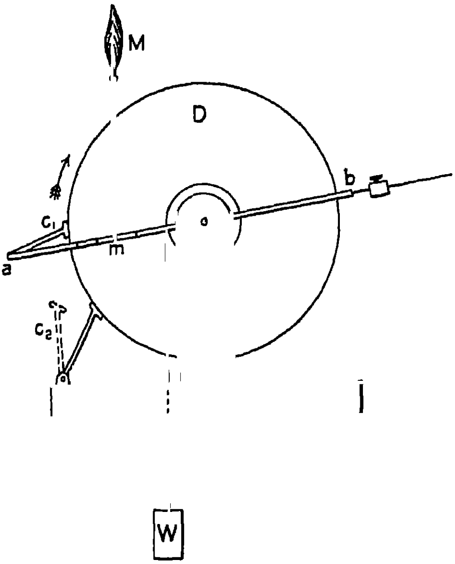


Diagram of Fick's 'Arbeitsammler' or muscle crank *a b* is a counterbalanced lever, attached to the muscle M at *m* When the muscle contracts, the catch *c* carries round the circumference of the wheel D and so coils up the weight W round the axle of the wheel When the muscle relaxes, if c_2 is in the situation of the dotted line, the weight pulls the wheel and lever back to its original position If, however, c_2 be applied to D, the backward movement of the wheel is prevented, and the muscle is extended simply by the weight of the lever *a b*. Thus at each contraction the weight is drawn a little higher, and external work is performed by the muscle the intact animal, in the dog fed on a pure flesh diet, Pfluger has calculated that the efficiency may be as great as 48 per cent. The efficiency of a heat engine is determined by the difference of absolute temperatures obtaining on the two sides of the machine; and since we cannot imagine even minutely localised changes of temperature in the animal body of more than a few degrees Centigrade, we must discard altogether the analogy of the steam engine, and seek some other explanation of the mechanism by which the muscle is enabled to transmute the chemical energy of its food into work or heat. It seems probable that the two products, heat and work, are simultaneous and independent in their origin, and that any proportion between them, therefore, is accidental. The muscle is, in fact, not a heat engine but a chemical engine. The chemical changes are converted directly into pressure changes leading to change of form of the ultimate contractile element, and it seems reasonable to suppose that these pressure changes are directly induced by the osmotic pressure of the products of chemical change produced as an immediate result of excitation.

SECTION 5

THE ELECTRICAL CHANGES IN MUSCLE

If a current from a battery be passed between two plates of platinum immersed in acidulated water or salt solution, *electrolysis* of the water takes place, bubbles of oxygen appearing on the positive plate (anode), and bubbles of hydrogen on the negative plate (kathode). If now we remove the battery, and connect the two plates (electrodes) by wires with a galvanometer, it will be seen that a current is passing through the galvanometer and water in the reverse direction to the previous battery current. This current is called the polarisation current, and is due to the electrolysis of the water that has taken place. The vessel in which the electrodes are immersed has in fact become a galvanic cell, the platinum covered with hydrogen bubbles being the positive *element*, and that covered with oxygen bubbles the negative *element*. Exactly the same process of electrolysis or polarisation takes place when we pass currents through the tissues of the body by means of metallic electrodes.

Hence before we can study accurately the delicate electrical changes that may occur normally in living tissues, it is necessary to have some form of electrodes in which this polarisation will not occur. The 'non-polarisable' electrodes which are most generally used for this purpose are made in the following way. A glass tube (Fig. 50) is closed at one end with a plug of kaolin made into a paste with a saturated solution of zinc sulphate. The rest of the tube is filled with a similar solution. Dipping into the zinc sulphate solution is a rod of pure zinc, amalgamated. Just before use, a plug of china clay made with normal saline solution is put on the end of the tube, so as to effect a connection between the zinc sulphate clay and the nerve or muscle which it is desired to stimulate or lead off. In these electrodes there is no contact of metals with fluids that can produce dissimilar ions (*e.g.* hydrogen or oxygen bubbles) at the surface of contact, and hence they may be regarded as practically non-polarisable.

A more convenient form is that devised by Burdon-Sanderson, in which the glass tube is bent into a U (Fig. 51). The mouth of the tube is closed by a smaller glass tube plugged with clay, and bearing a plug of normal saline clay.

If a muscle such as the sartorius be removed from the body, and two non-polarisable electrodes connected with a delicate galvanometer be applied to two points of its surface, there will be a deflection of the mirror attached to the galvanometer, showing the presence of a current in the muscle from the ends to the middle, and in the external circuit from the middle (or equator) to the ends. It was formerly thought that this current was always present in all normal muscles, and it was spoken of as the 'natural muscle current;' the muscle was said to be made up of a series of electromotive molecules, the equator of each molecule being positive to the two poles (Du Bois Reymond). It has been conclusively shown however (by Hermann and others) that this current of resting muscle is not a natural current at all, but is due to the effects of injury in making the preparation. The less the preparation is injured, the smaller is the current to be obtained from it, and in some contractile tissues, such as the heart, there may be absolutely no current during quiescence.

FIG. 50.

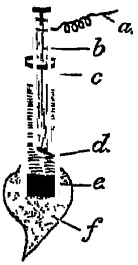


FIG 51

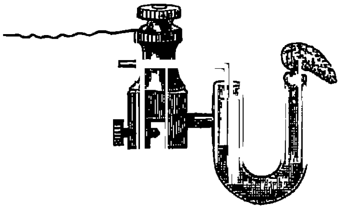


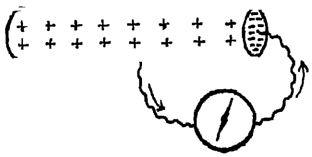
FIG. 50 —Diagram of non-polarisable electrode *a* Covered wire *b* Amalgamated zinc rod. *c* Glass tube *d.* Saturated ZnSO solution *e.* Plug of zinc sulphate clay *f* Plug of normal saline clay

FIG. 51 —U-shaped non-polarisable electrodes

Hermann describes the fact of the existence of currents of rest thus:—'In partially injured muscles every point of the injured part is negative towards the points of the uninjured surface.' Fig. 52 shows the direction of the current in a muscle with two cut ends.

When the whole muscle is quite dead, this current of rest, or 'demarcation current' (Hermann), disappears. The current is due to the electrical differences at the junction of living and dying (not *dead*) tissue. If the sartorius of the frog be cut out and immersed for twenty-four hours in 0·6 per cent. NaCl solution made with tap water (*i.e.* containing lime), all the injured fibres die, and the uninjured fibres are then found to be iso-electric and therefore currentless.

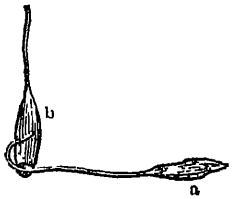
Fig. 52.



Current of rest

The existence of this current may be demonstrated without using a galvanometer If the nerve of a sensitive muscle-nerve preparation (a, Fig. 53) be allowed to fall on an excised muscle (b), so that two points of the nerve are in contact with the cut end and with the surface of the second muscle (b), the muscle (a) will contract each time the nerve touches (b) so as to complete the circuit.

Fig 53.



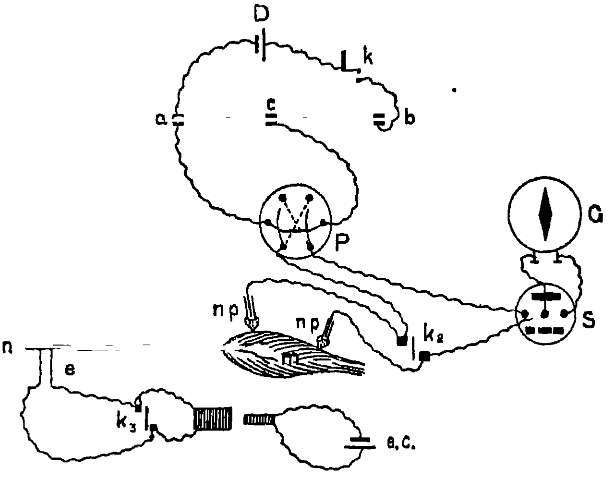
Rheoscopic frog.

Whatever be the explanation of this current of resting muscle, there is no doubt that a very definite electrical change occurs in a muscle when it contracts.

To show this change, we may lead off two points, one on the cut end and one on the surface of the muscle of a muscle-nerve preparation, to a galvanometer. We shall then obtain a deflection of the mirror of the magnet, due to the current of rest or demarcation current. If now the nerve be stimulated with an interrupted current so as to throw the muscle into a tetanus, the ray of light from the galvanometer mirror is observed to swing back towards the zero of the scale, showing that the current which was present before is diminished. When the excitation of the nerve is discontinued, the galvanometer indicates once more the original current of rest. This diminution of the current of rest during activity of a muscle is spoken of as the '*negative variation.*'

In carrying out this experiment it is usual to compensate the demarcation current by sending in a small fraction of the current from a constant cell. The arrangement of the apparatus is represented in the accompanying diagram. Two non-polarisable electrodes (np) are applied to the surface and cross-section of a muscle (m). These are connected with the shunt of the galvanometer, one of the wires however being connected with a Pohl's reverser (P), and this in its turn with the shunt (S). The two end terminals of the reverser are connected with a rheochord, through the wire of which (A, B) a constant current is passing from the Daniell cell (D) By means of the rider (c) the fraction of current passing through the reverser can be modified to any extent. The key (k) being open, the muscle is connected with the shunt and galvanometer, and the direction and extent of the swing noticed The key (k) is then closed, and by means of the reverser the current is sent through the galvanometer in the *opposite* direction to the demarcation current, and the rider (c) shifted until the two currents exactly balance each other, and the

Fig. 54.



needle of the galvanometer returns to zero of the scale. This adjustment is first made, using only $\frac{1}{1000}$ of the total current, and then by means of the shunt, $\frac{1}{100}$, $\frac{1}{10}$, and finally the whole current is thrown into the galvanometer. If this precaution be not taken, much too large a current may in the first case be sent through the galvanometer, to the detriment of the instrument If we know the difference of potential between the two ends of the wire, the proportion $\frac{ac}{ab}$ will give us the E M.F of the demarcation current The galvanometer needle having by compensation been brought to zero, stimulation of the nerve at (e) by interrupted currents causes the needle to swing at once in the opposite direction to the first variation This swing is the measure of the negative variation or current of action

The negative variation may also be observed, by means of a very lightly moving galvanometer, to accompany a single twitch of the muscle. It has been found to occupy about $\frac{1}{200}$ second, and to occur immediately after stimulation.

Since a delicate galvanometer takes some seconds to come to rest when a current is sent through it, the whole of the variation is over at a time when the magnet has hardly commenced its swing Hence to analyse more fully the electrical change accompanying each separate twitch of the muscle, recourse must be had to other methods than the direct galvanometric method.

For this purpose we generally use an instrument called the rheotome, by which we can connect the electrodes on the muscle with the galvanometer at

Fig 55.

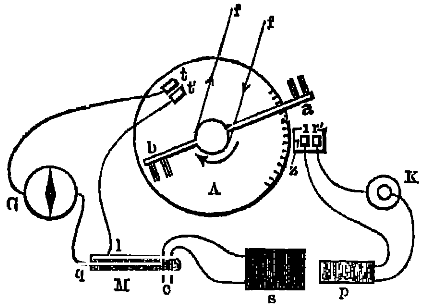


Diagram of rheotome (Hermann).

varying intervals after stimulation, and by observing the galvanometer readings at each $\frac{1}{1000}$ second after stimulation, can map out the exact course of the current of action

The instrument is represented diagrammatically in Fig 55

By means of a clock or motor the rod, a b, is made to rotate at any required rate round a vertical axis at its centre On either end it carries two brushes made of fine wire and connected together The brushes at each rotation come in contact with the pieces of copper, r r', and when this happens the primary circuit, k, r', a, r, p, is rapidly closed and broken again, thus giving rise to a momentary current in the secondary coil, B, and exciting the muscle, M In the same way the brushes, b, close the galvanometer-electrode-muscle circuit, G, t, b, t′, i, M, q, each time they brush on the copper banks, t t′ By turning the disc, A, round, the interval at which the brushes, b, pass t t′, after the brushes, a, pass i i′, can be altered at will, and therefore the interval between stimulation and leading off the current to the galvanometer

But there is no need for any demarcation current to be present in order to show an electrical change accompanying contraction. In fact we learn much more about the nature of the excitatory change if we study the electrical behaviour of a perfectly normal (and therefore currentless) muscle on stimulation. This can be easily done by means of the rheotome or capillary electrometer.

If a perfectly uninjured regular muscle (such as the sartorius) be stimulated with a single induction shock at one end (x) (Fig. 56), and the relative electrical conditions of the points (a) and (b) investigated, it will be found that as soon as the excitatory process reaches (a), this point becomes negative to (b), and there is thus a current in the galvanometer from (b) to (a). A moment later the two points are equipotential, as shown by the fact that no current passes through the galvanometer. A thousandth of a second later this balance is upset, and now (b) is negative to (a), and the galvanometer needle swings in the opposite direction.

Fig 56

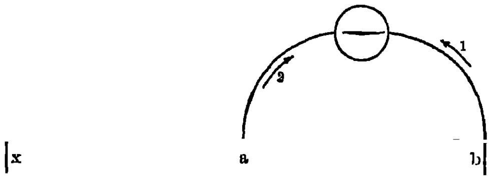


Diagram showing diphasic variation of uninjured muscle

Thus every excitation of a normal muscle gives rise to a diphasic variation, of such a direction that the point stimulated first becomes negative[1] to all other points of the muscle, and this 'negativity' (to use a loose but convenient expression) passes as a wave down the muscle, accompanying or preceding the wave of contraction, and travelling at the same rate.

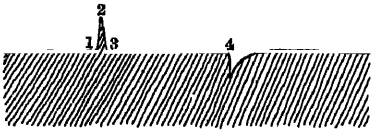
---

[1] The statement that the excited portion of the muscle becomes 'negative,' though sanctioned by long usage, is not very exact and may give rise to misconception When we lead off the terminals of a copper zinc couple or cell to a galvanometer, a current flows outside the cell from copper to zinc and inside the cell from zinc to copper. In this case we know that the zinc is electro-

This diphasic current of action is shown much more clearly and easily on a slowly contracting tissue such as the frog's ventricle.

Fig. 57 represents the photograph of the variation of the frog's heart, as shown by a capillary electrometer, one terminal (acid) of which is connected with the base of the ventricle, and the other (Hg) with the apex. The contraction of the ventricle begins at the base. The base therefore becomes negative, and the column of mercury moves up (1 to 2) A moment later the contraction has extended to the apex. There is now an equalisation of the potential between the two terminals, so the mercury comes back quickly to the base line. Here it stops for about one and a half seconds. During this time the whole heart is contracting equally; both base and apex are thus in a similar condition, and there can be no difference of potential between them. The contraction then goes off, but the relaxation, just as the contraction, begins at the base, and proceeds thence to the apex. There is thus a small period in which the apex

FIG 57



Tracing of diphasic variation of frog's heart taken with capillary electrometer

positive to the copper, and in the same way we must assume that the excited portion of a muscle is really *electropositive* to the unexcited portions When therefore we speak of any part of a tissue being negative, we are using a conventional expression to indicate the direction of the current in the outer circuit, and not the electrical condition of the tissue itself. In order to avoid the confusion which might result from an attempt to replace the loose expression 'negative' by the correct expression 'electropositive,' Waller has suggested the employment of the term 'zincative' to indicate the electrical condition accompanying excitation This term also serves to emphasise the fact that the excited portion, like the zinc in a zinc copper cell, is the chief seat of chemical change.

is still contracted while the base is relaxed, and the apex is therefore negative to the base. This terminal negativity of the apex is shown on the photograph by the excursion of the column of mercury away from the point of the capillary at (4).

The only difference between the electrical changes in this case and in that of voluntary muscle is that in the latter all processes are very much quicker, so that as a rule the point (a) (Fig. 56) has ceased to be negative before the negativity of (b) has attained its full height, and there is thus no prolonged equipotential stage.

Fig 58

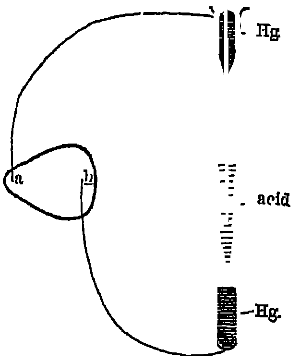
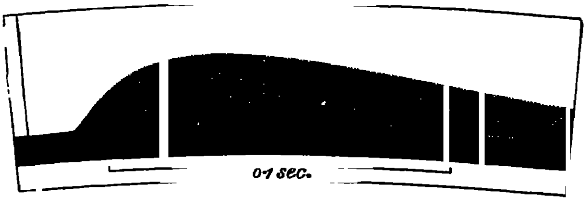


Diagram of capillary electrometer Hg, Mercury The two terminals are represented as leading off two points at the base and apex of a frog's heart, a b

Although in the case of the slowly contracting ventricle of the tortoise, the record obtained of the electrical changes accompanying its contraction by means of the capillary electrometer shows with great clearness the diphasic nature of the variation, and therefore the wave character of the electrical change, considerable difficulty is at first experienced when we attempt to interpret in the same way the electrometer record of the electrical response of voluntary muscle In this case the electrical change at any spot only lasts about $\frac{1}{200}$ of a second, and there is not a prolonged equipotential period, as in the case of the heart The diphasic nature of the variation is however obvious, if we compare the electrometer record of an intact and therefore currentless muscle with that of the change produced by a single stimulus in a muscle in which one of the leading-off points has been injured, so as to give rise to a demarcation current. The two curves are given in Fig 59, the upper shadowy tracing being that obtained from the injured muscle It will be seen that the distinguishing character of a diphasic variation in the rapidly contracting striated muscle consists in the fact that the downstroke of the image of the meniscus is as rapid as the upstroke, whereas the monophasic variation of the injured muscle presents a slow fall produced by the gradual leakage of the charge imparted to the instrument back through the electrodes and muscle. Knowing the constants of the instrument used, it is possible, by measuring the curvature of this 'spike,' as the record of the diphasic variation is termed, to determine accurately the electromotive force of the action current producing the excursion of the electrometer. An exactly similar curve can be obtained by putting in a current of similar E M F. from a battery, first in one direction for $\frac{1}{200}$ of a second, and then in a reverse direction for another $\frac{1}{200}$ of a second

It must be remembered that a diphasic variation does not mean that one part of a muscle changes from normal in one direction, and then swings back past the normal in another direction, but that a change in one direction at one electrode dies away and is succeeded by a similar change in the same direction, which also dies away, at the second electrode that is to say, a diphasic variation implies a progression of a wave of electrical change between the leading-off points It is found that the rate of transmission of this electrical change in muscle is exactly the same as the rate of propagation of the wave of contraction, and amounts at ordinary temperatures to about 3 metres per second.

FIG. 59.



Superimposed photographs of the electrical variation of the sartorius in response to a single stimulus. (Burdon-Sanderson)

We may now return for a moment to the consideration of the current of rest observed in injured muscle.

Heimann considers that muscle (or contractile tissue) becomes negative under two conditions :

(1) In activity.

(2) When dying.

But it must be confessed that the second may be easily placed under the first head. Section or injury of a muscle causes a constant stimulation of the adjacent parts. These parts therefore become negative to the other parts that are further away from the seat of injury, and we thus get a demarcation current. Hence we come to the conclusion (only paradoxical in terms) that the currents of rest are currents of action, and are due to excitation around the injured spot.[1]

Electrical Organs

An interesting light has been thrown on this question by a study of the electrical organ in the torpedo and other electric fishes. In the torpedo is found on each side of the middle line a kidney-shaped organ forming a considerable mass of the body-substance and extending from dorsal to ventral side. Viewed from the surface each organ presents a honeycombed appearance, due to the fact that it is made up of a number of prismatic columns running dorso-ventrally, each column consisting of an enormous number of hexagonal discs placed one above the other. Each column is richly supplied with nerves, which are derived from large ganglion cells, situate in a distinct lobe of the brain. Each nerve divides up into eighteen or twenty branches as it approaches the column, as shown in the diagram (Fig. 60). Each plate receives nerve-fibres at all its six corners. On tracing the nerve-fibre into the plate, we find that every element consists practically of a gigantic motor end-plate. The axis-cylinders branch dichotomously and form a close network embedded in granular protoplasm, and resting on a granular material which represents all that is left of the striated muscles of the embryo, out of which the electrical organs have been developed. We have therefore a series of end-plates separated from one another by laminæ of connective tissue, and so arranged that any electrical changes in the nerve terminations will be summated somewhat after the analogy of the summation of effect in a Volta's pile. As a result we find that, although the electromotive force of the action current in a single element is only about 0·025 volt (no greater than that observed in an ordinary nerve or muscle), yet the E.M.F. of the whole organ compounded of thousands of these plates attains to several hundred volts, so that, in spite of the short circuiting of the current by the water in which the animal is immersed, a discharge of the organ would give a painful shock to any one touching the fish, and may even kill small animals.

---

[1] If the demarcation current is really only due to excitation, we should expect to find it weaker than the action current obtained by exciting the whole muscle to contract And this is the case The E M F of the demarcation current of a sartorius equals about 0 05 of a Daniell cell The action current of the same muscle may attain to an E M F =0 08 of a Daniell cell (Gotch)

We have here an excitable tissue in which the action current is from the anatomical arrangements of the organ always monophasic. If an organ or segment of an organ be cut out of the body, it will be found to present a resting current, which however declines quickly and may finally disappear altogether. The direction of this resting current is always the same as that of the discharge. Injury to any part of the organ or at either electrode always increases the resting current, whereas of course in a muscle the direction of the resting current is entirely determined by the situation of the injury. In the torpedo therefore the resting current is always a current of action due to the slight constant irritation of the injury; and there seems no reason why we should assume a different explanation for the resting current in striated muscle or in nerve.

FIG 60

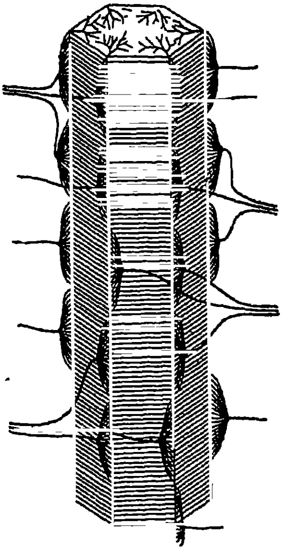


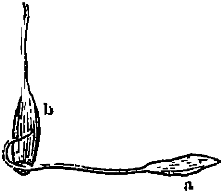
Diagram of the structure of a column of the electrical organ of the Torpedo, showing its division into discs, and the distribution of its nerve supply (Fritsch)

Secondary Contraction. Rheoscopic Frog

The negative variation of one muscle may be used to make another contract.

If the nerve of the preparation (a) (in Fig. 61) be laid so as to touch at two points the cut end and surface of the muscle (b), and the nerve of (b) then stimulated with single induction shocks, every contraction of (b) will be attended by a contraction of (a), excited by the negative variation of the current passing through its nerve from the point touching the cut end to that in contact with the equator of (b).

FIG. 61



Rheoscopic frog

If the nerve of (b) is tetanised, (a) as well as (b) enters into a continued contraction. This '*secondary tetanus*' is of interest as showing that, although the contractions of (b) are fused, the excitatory process and negative variations are still quite distinct.

SECTION 6

THE CHEMISTRY OF MUSCLE

Chemical Composition of Voluntary Muscle

It is impossible to speak with certainty about the chemical composition of any living tissue, since in the act of analysis we destroy the life of the tissue; all we can do in most cases is to find the proximate principles present in the dead tissue. But, by using certain precautions, we may learn some interesting facts about the chemistry of living muscle. Muscle of cold-blooded animals may be cooled below 0° C. without losing its irritability on re-warming and therefore we may say without its life being destroyed. If the living muscle of frogs be frozen, then minced with ice-cold knives as finely as possible and pounded in a mortar with four times its weight of snow containing 0·6 per cent. of common salt, and the mixture thrown on to a filter and kept at a little over 0° C., an opalescent fluid filters through. The filters soon get clogged and therefore must be frequently changed. Their temperature must not be allowed to rise over 2° or 3° C. This fluid is called muscle-plasma. If its temperature be allowed to rise to that of the room, it clots, and the clot soon contracts, squeezing out a serum, just as in the case of blood-plasma.

The muscle-plasma is neutral or slightly alkaline. When coagulation takes place however, it becomes distinctly acid, and this acidity has been shown to be due to the formation of sarcolactic acid in the process.

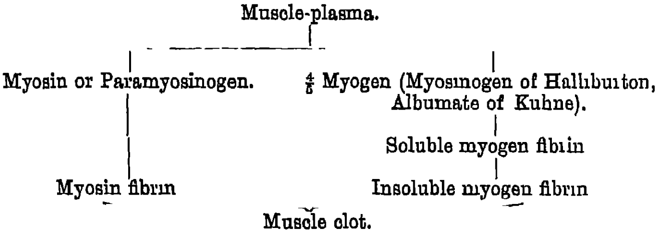
Arguing chiefly from analogy with the blood-plasma, the muscle-plasma has been said to contain a body, myosinogen, which is converted when clotting takes place into myosin, and perhaps other bodies, of which lactic acid may be one.

The exact nature of the proteins in muscle-plasma, as well as of the protein constituent of the clot, which we have called myosin, is still a subject of debate Kühne, to whom we owe our first acquaintance with muscle-plasma, described the clot as consisting of myosin, a globulin, soluble in 5 per cent solutions of neutral salts, such as $NaCl$ or $MgSo_4$, precipitated by complete saturation with $MgSo_4$, and coagulated on heating to 56° C In the muscle serum, obtained after separation of the clot, he found three proteins, one coagulating at 45° C., one he called an albumate (*i.e* a derived albumen), and the third coagulating about 75° C, and apparently identical with serum albumen. Halliburton extended these researches to the muscles of warm-blooded animals He described four proteins as existing in muscle-plasma, of which two, paramyosinogen and myosinogen, gave rise to the clot of myosin.

In no case however is it possible to entirely dissolve up the clot when once formed, and it seems that the so-called solution in dilute salt solutions was merely an extraction of still soluble proteid in the meshes of the clot The latest work on the subject by von Furth has shown that if the muscles of a mammal are washed free of adherent lymph and blood, the plasma obtained by extraction with normal salt solution contains only two proteins. These proteins are extremely unstable, and are gradually transformed on standing into insoluble protein, giving rise to a precipitate in dilute solutions, or forming a jelly-like clot in strong solutions. The properties of these proteins may be summarised as follows:

1. Myosin (paramyosinogen of Halliburton) A globulin, coagulating at about 47°-50° C, precipitated by half saturation with ammonium sulphate or on dialysis Transformed slowly in solution, rapidly on precipitation, into an insoluble protein, myosin fibrin.

2 Myogen (myosinogen of Halliburton). A protein allied to the albumens in that it is not precipitated by dialysis Coagulates on heating at 55°-60° C. It changes slowly into an insoluble protein, myogen fibrin, but *passes through an intermediate soluble stage* called soluble myogen fibrin This latter body coagulates on heating to 40° C, being instantly converted at this temperature into insoluble myogen fibrin It does not seem that any ferment action is associated with these changes, which we may represent by the following schema



Soluble myogen fibrin, which in mammalian muscle-plasma forms only on standing, exists apparently preformed in frog's muscle Hence the instantaneous clotting of frog's muscle-plasma on warming to 40° C

The residue left after the expression of the muscle-plasma consists chiefly of connective tissue, sarcolemma, and nuclei, and as such contains gelatin (or rather collagen), mucin, nuclein, and adhering traces of the proteins of the muscle-plasma itself.

The muscle serum contains the greater part of the soluble constituents of muscle. These are—

A. *Colouring matters.*—All red muscles contain a considerable amount of hæmoglobin. In many, a special pigment, probably allied to hæmoglobin, is also present. This has been named *myohæmatin* (MacMunn).

B. *Nitrogenous extractives.*—Of these, the most important is creatin ($C_4H_9N_3O_2+H_2O$), which occurs to the extent of 0·2 to 0·3 per cent. This substance is found only in muscular and nervous tissues. Its significance we shall discuss later on when inquiring into the history of the formation of urea.

Other nitrogenous extractives are—

Hypoxanthin or sarcin, xanthin (both bodies allied to uric acid), carnin, and a trace of urea.

C. *Non-nitrogenous constituents.*—Fats.

Glycogen. The amount of this is very variable. In the embryo the muscles may contain large quantities, but in the adult they contain only from 0·4 to 1 per cent.

Inosit ($C_6H_{12}O_6+2H_2O$), or 'muscle-sugar,' which occurs in minute traces, is non-fermentable, does not rotate polarised light, and does not reduce Fehling's solution. It does not belong to the group of carbohydrates at all, being a derivative of benzene.

Dextrose. It is doubtful whether this is present in fresh resting muscle.

D. *Inorganic constituents.*—Muscle contains about 75 per cent. of water. The ash forms 1 to 1·5 per cent. and consists chiefly of salts of potassium and phosphoric acid. There are small traces of calcium, magnesium, chlorine, and iron.

Rigor Mortis

All muscles, within a short time of their removal from the body, or if left in the body after general death, lose their irritability, and this is succeeded by an event which occurs rather suddenly, and is known as rigor mortis. The muscle, which was before translucent, supple, extensible, becomes more opaque, rigid, and inextensible, and shortens. The shortening is not very powerful, and can be prevented by loading the muscle moderately Chemical changes also take place. The muscle, which was previously alkaline, becomes distinctly acid, the acidity being due to the formation of sarcolactic acid. There is also pruduction of CO_2 and an evolution of heat.

It is generally believed that this change is identical with the clotting of muscle-plasma, and that the rigidity as well as the contraction of the muscle is due to the coagulation of the muscle-proteins. That there is at any rate a close connection between the two sets of phenomena is shown by Brodie's observations on the heat-contraction of muscle. This observer found that, if a living muscle be lightly loaded and then warmed very gradually, a series of stages in the heat-contraction could be distinguished corresponding to the coagulation temperatures of the different proteins described by von Furth in muscle-plasma.

The onset of rigor is closely connected with the post-mortem production of sarcolactic acid. If the formation of this acid be prevented or diminished (as may be effected by keeping the muscle in an atmosphere of pure oxygen), rigor may be retarded or prevented altogether. The same result is obtained if the accumulation of the acid in the muscle is prevented by washing out its blood vessels with a slightly alkaline normal saline solution. Under these circumstances, the muscle gradually loses its irritability, and may finally be regarded as dead, but it will then begin to putrefy without at any time showing any signs of rigor. The influence of lactic acid in causing the coagulation of muscle proteins, distinctive of rigor mortis, is shown by the fact that after severe muscular fatigue, as in hunted animals, where there has already been a considerable formation of these waste products of muscular contraction, rigidity may come on almost immediately after death. Rigor mortis therefore may be regarded as a coagulation of muscle proteins induced by the accumulation of the products of metabolism in the surviving excised muscle. Of course, a rigidity of muscle may be also brought about by the direct agency of heat, as by plunging into boiling water. In this case there has been no time for any chemical change to take place, and the scalded muscle remains, like fresh muscle, slightly alkaline to litmus.

A rigid muscle never recovers. It is dead, and in dying chemical and physical changes have taken place, giving rise to shortening and rigidity, and converting a fluid complex substance into an aggregate of insoluble protein, with the formation of CO_2 and lactic acid. The unstable living molecule has broken down into dead stable molecules, the potential energy of the former appearing as heat and work

The lactic acid formed in muscle (sarcolactic acid) is a physical isomer of the lactic acid formed in the fermentation or souring of milk They both have the formula $CH_3CH(OH)COOH$, i e they are ethylidene lactic acids. The lactic acid of fermentation is optically inactive; sarcolactic acid rotates polarised light to the right, while a third isomer which is lævorotatory is produced by the action of various bacilli and vibriones on cane sugar.

The Chemical Changes which accompany Activity

The principle of the conservation of energy teaches us that the energy of the contraction of muscle must be derived from chemical changes, probably processes of decomposition and oxidation, occurring in the muscle itself. In seeking out the nature of these changes, three methods are open to us:

1. We can examine the changes in the muscle itself, avoiding so far as possible reintegrative changes by working on excised muscles.

2. We can investigate the changes in the medium of the muscle. Muscle may be exposed in a vacuum or in a confined space of air, and its gaseous interchanges during rest and activity compared. Or we may lead a current of defibrinated blood through excised muscles, and determine the change in the composition of the blood before and after passing through the muscle under various conditions.

3. A method which, although apparently complex, has rendered the utmost service to the physiology of muscle, is to use the changes in the total metabolism of the animal during rest and muscular work as a clue to the muscular metabolism itself. In such a case the respiratory exchanges of the animal are determined (viz its oxygen intake and its CO_2 output), and the urine and fæces are carefully analysed, in order to judge of the action of muscular work on the carbon and nitrogen metabolism of the body.

By one or other of these methods it has been found that the main products of muscular activity are the same as those which are produced during the death of a muscle, viz. sarcolactic acid and carbon dioxide.

It was shown long ago by Helmholtz that when a muscle was tetanised to exhaustion, the total amount of its watery extractives diminished, while the amount of its alcoholic extractives increased; and there is no doubt that part of this difference is due to the formation of lactic acid. The souring of muscle during activity can be easily demonstrated by stimulating the muscle for some time and then crushing a fragment of the excised muscle on litmus paper. The litmus is at once turned red. Or we may inject a solution of acid fuchsin under the skin of a frog, and the next day expose a sciatic nerve and stimulate it for fifteen or twenty minutes. On skinning the hind legs, a difference in colour will be at once apparent, the leg which has been active being of a deep rose colour, owing to the action of the acid on the fuchsin.

Sarcolactic acid is not present in a free state in muscle, the acidity being, like that of urine, due to the presence of acid phosphates. The sarcolactic acid can be extracted from the muscle by means of alcohol. It is generally separated in the form of the zinc sarcolactate, by boiling its partially purified solution with zinc carbonate Its presence may be tested for by means of Uffelmann's reagent, which is made by the addition of ferric chloride to dilute carbolic acid The purple solution thus produced is at once changed to yellow by the addition of even traces of lactic acid

We get a similar formation of lactic acid in excised mammalian muscles, which are kept alive by an artificial circulation. We do not know how far the formation of lactic acid occurs under normal circumstances in the living body. At all events any lactic acid produced by the muscle during activity in the normal animal, is further transformed (to CO_2) before it leaves the body. During severe muscular exercise however, lactic acid may be formed in the muscles and escape oxidation in the body, so that it is excreted in the urine.

The second substance, carbon dioxide, is continually being formed by all living tissues, and is the end-product of practically all the carbon metabolism of the body. If a muscle be hung up in a confined space, it will be found to take up oxygen and give off CO_2; and these interchanges are quickened by causing the muscle to contract.

It is found however that this effect of activity is dependent on the composition of the gas surrounding the muscle If it be hung up in a vacuum or in an atmosphere of nitrogen or hydrogen, there is a slow evolution of CO_2, which is not appreciably quickened during contraction, and seems to be conditioned by a gradual driving off of CO_2 from the alkaline carbonates in the muscle, as a result of the steady production of lactic acid which precedes the onset of rigor. If however the muscle be suspended in an atmosphere of pure oxygen, the formation of acid is diminished or abolished; but now each contraction of the muscle is followed by an increased evolution of carbon dioxide.

We see therefore that, according to the environment of the muscle, its activity is attended by the formation either of lactic acid or of carbon dioxide, the latter substance being the sole product if sufficient oxygen be supplied to the muscle. If the supply of oxygen be inadequate, both substances are produced, the proportion of lactic acid varying according to the relative inadequacy of the oxygen supply. This relation holds good both in rest and activity, the effect of activity being merely to increase the chemical changes which are going on spontaneously in the surviving resting muscle.

It is an interesting point to determine whether we have here really two alternative chemical mechanisms for the production of energy. We know that sugar can be utilised by muscle as a food and source of energy. It has been suggested therefore that, in the absence of oxygen, the energy for contraction was derived from a process of disintegration, each molecule of grape sugar breaking down into two molecules of lactic acid, thus:

$$\underset{\text{Sugar}}{C_6H_{12}O_6} = \underset{\text{Lactic acid}}{2C_3H_6O_3}.$$

On the other hand, in the presence of sufficient oxygen, the sugar would be entirely oxidised with the formation of CO_2 and water, thus:

$$\underset{\text{Sugar}}{C_6H_{12}O_6} + 6O_2 = 6CO_2 + 6H_2O.$$

The change from sugar to lactic acid involves, however, practically no evolution of energy—so that in the absence of oxygen the energy of contraction must be derived from some other source.

It seems more probable that we are dealing here with two stages of one process, and that in the muscle under normal conditions (*i.e.* richly supplied with oxygen) the first chemical change is one of disintegration, leading to the formation of lactic acid (and probably other substances), and that this is followed by a process of oxidation, in which all the products of the first stage are converted into CO_2, which can be rapidly eliminated from the muscle. If the supply of oxygen is deficient, the products of the first stage remain in the muscle, giving rise to the phenomena of fatigue, and finally inducing the coagulation of the muscle proteins which determines rigor mortis.

We may therefore conceive of the living protoplasm of the muscle during contraction as using stored-up carbohydrate or allied substances, and oxygen to furnish the necessary energy; but it is also possible that the whole living molecule breaks down with the formation of a still living protein residue, and waste products such as CO_2 and lactic acid. Immediately afterwards this living residue takes up oxygen and carbon-containing substances from the surrounding lymph or interstitial substance of the muscle, and is ready once more to break down and furnish energy in the process.

A hypothetical muscle molecule of this nature is spoken of as *inogen*.

The facts, that the main products of muscular activity are CO_2 and lactic acid, and that no change has been found to occur in the creatin or other nitrogenous extractives of the muscle during contraction, have produced a widespread idea that the sole source of muscular energy is to be sought in the combustion of carbohydrate or fatty material, the proteins of the body taking no part in the process. The whole question will have to be discussed more fully later on, when dealing with the general metabolism of the body. I may say here however that, so far as the evidence goes, we cannot draw any qualitative distinction between the metabolism which results in muscular work, and the metabolism of the resting animal. Thus the relative proportion of the CO_2 produced to the oxygen taken in, the so-called respiratory quotient $\frac{CO_2}{O_2}$, will vary according to the food that is being consumed, being unity with carbohydrates, less than unity with proteins, and still less with fats. It is found that muscular work does not alter the respiratory quotient · *i.e.* during work the qualitative metabolism of the whole body is the same as during rest. We must conclude therefore that the muscle derives its energy from the combustion of all three classes of foodstuffs, although in the absence of excess of food, it will perform its work at the expense of stored-up fat or carbohydrate.

The absence of change in the respiratory quotient during exercise shows moreover that in a muscle under normal conditions the two processes, viz. the taking in of oxygen and the giving out of CO_2, keep pace one with the other. In warm-blooded animals, the shutting off of the oxygen supply rapidly induces paralysis and loss of irritability of the muscles. This fact, coupled with the fact that, as mentioned above, the final results of muscular activity differ according as the muscle is or is not supplied with oxygen, suggests that the oxygen takes part in the process of activity only at a late stage, after the disintegration of the complex living molecule has already begun.

Such a conclusion is, however, opposed to the generally accepted views on the nature of the oxidation processes in the cell According to Hermann, Pfluger, Verworn and others, there is during rest a building up both of oxygen and food material into the living molecule Activity consists in a rearrangement of the molecule, with the assumption of more stable positions by the oxygen and carbon atoms, and a consequent production of CO_2 (Cp the explosion of gun-cotton or nitroglycerin). The presence of this intramolecular oxygen in an unstable position would be a necessary condition both for irritability as well as for the activity of all forms of living tissue, espec muscle and nerve

If the muscle can use all classes of foodstuffs in its metabolism, one would expect to find some change in the nitrogenous constituents as the result of activity. Physiologists have searched in vain however for any evidence of the formation of creatin or urea in excised muscle during contraction. Schöndorff has recently shown that if excised muscle be kept alive by perfusion of defibrinated blood, its activity is associated with increased formation of ammonia. The formation of ammonia is however the natural mode of protection of the whole organism against acid poisoning, and it seems quite probable that in Schondorff's experiments the ammonia formation was simply a secondary result of the lactic acid formation, and not a direct expression of the metabolism of the active muscle.

SECTION 7

CONDITIONS MODIFYING THE IRRITABILITY AND CONTRACTION OF MUSCULAR TISSUE

Temperature

Speaking generally, the effect of warming a muscle is to quicken all its processes. The latent period becomes shorter and the muscle curve steeper and shorter.

It is very often observed that the height of contraction of the warmed muscle is greater than that obtained at ordinary temperatures It seems that this apparent increase in height is really instrumental in origin, the quicker-moving muscle jerking the lever beyond the real extent of the contraction. If proper means are taken to eliminate this overshooting of the lever, it is found that the height of contraction is unaltered between 5° and 20° C, the only change being in the time-relations of the curves

If a muscle be heated gradually (without stimulation) up to about 45° C., it begins to contract slowly at about 34° C., and this contraction reaches its maximum at 45° C., at which point the muscle has entered into pronounced rigor mortis.

Cold has the reverse effect. The intra-molecular processes which lie at the root of the muscular activity are slowed, so that the latent period as well as the contraction period is prolonged. Curiously the action of cold on the excitability of muscle is to increase it, so that any form of stimulus is more effective at 5° C. than at 25° C. Moreover, when maximal stimuli are being used, and the muscle is heavily loaded, the first effect of the application of cold may be to increase the height as well as the duration of contraction, for the same reason that a gentle prolonged push is more efficacious in closing a door than would be a heavy blow with a hammer.

If however a muscle be cooled for a short time to zero or a little below, it loses its irritability, which returns if the muscle be gradually warmed again.

Prolonged exposure to severe cold, sufficient to cause the formation of ice in the muscle fibres, irrevocably destroys its irritability. Warming the muscle now will simply bring about rigor mortis.

Fatigue

A muscle will not go on contracting indefinitely. If it be repeatedly stimulated, changes soon become apparent in the curve of contraction. The latent period is prolonged, as well as the length of the contractions; the absolute height and work done are diminished. At the same time the muscle does not return to its original length; the shortening which remains is spoken of as '*contraction remainder.*'

After an initial rise during the first few contractions these diminish uniformly in height till they are no longer apparent, so that the muscle is now said to have lost its irritability.

FIG 62

Muscle curves showing fatigue in consequence of repeated stimulation The first six contractions are numbered, and show the initial increase of the first three contractions. (Brodie)

At the same time there is a great prolongation of the curve, occasioned almost entirely by a retardation of the relaxation, so that after forty or fifty contractions several seconds may elapse before the lever returns to the base line.

The fact that the relaxation part of the muscle curve is affected by various conditions, especially fatigue, apparently independently of the contraction part, led Fick to put forward a theory that two distinct processes were concerned in the response of a muscle to excitation, one process causing the active shortening and the other the relaxation. (It must be noted that this is *not* the same as saying that the *lengthening* is an active process, a statement negatived by the behaviour of a muscle when caused to contract on mercury) He suggested that the disintegration associated with activity might be conceived as occurring in two stages the first resulting in the production of sarcolactic acid and the active shortening of the muscle; the second in the further conversion of the acid into

CO_2, with a consequent relaxation. A retardation of this second phase would cause the prolonged curve with 'contraction remainder' observed in a fatigued muscle The absence of any appreciable evolution in the conversion of glucose to lactic acid, shows however that the formation of lactic acid cannot represent the whole of the chemical changes involved in the phase of shortening

If left to itself, the muscle which has been exhausted by repeated stimulation will recover. The recovery is hastened by passing a stream of blood, or even of salt solution, through the blood-vessels of the muscle. Recovery however in a muscle outside the body is never complete.

The phenomena of fatigue probably depend on two factors:

(1) The consumption of the contractile material or the substances available for the supply of potential energy to this material.

(2) The accumulation of waste products of contraction. Of these waste products the lactic acid is of great importance. Fatigue may be artificially induced in a muscle by 'feeding' it with a dilute solution of lactic acid, and this again removed by washing out the muscle with normal saline solution containing a small percentage of alkali. After a certain time the mere removal of waste products by means of an artificial circulation of salt solution becomes inadequate to restore contractile power to the muscle. In this case the muscle can be made to contract once more by supplying it with fresh food material, as by the circulation of serum or diluted blood.

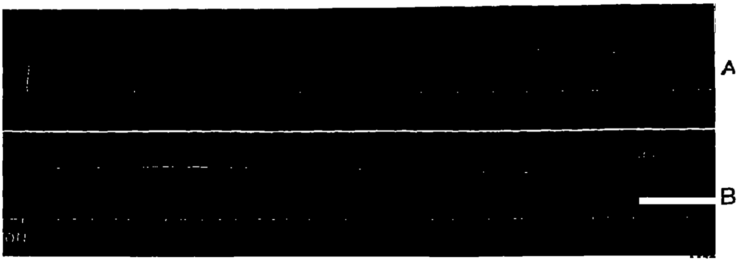
The Action of Drugs upon Voluntary Muscle

Of the drugs that have a direct action on muscle, the most remarkable is veratrin, which causes an excessive prolongation of a muscular contraction (produced by a single stimulus). Thus the 'twitch' of a muscle poisoned with veratrin may last fifty or sixty seconds, instead of the normal one-tenth of a second (Fig. 63).

Barium salts have a similar though less marked effect.

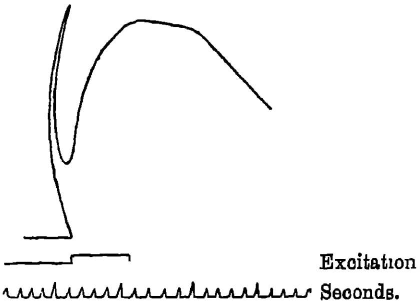
In order to carry out the poisoning with veratrin, very weak solutions (1 in 100,000 or 1 in 1,000,000 of normal saline) should be used and the muscle exposed to its action for some hours. We get then on a single stimulus a response lasting many seconds and exactly similar in height and form to a tetanus obtained by discontinuous stimulation. If stronger solutions be used, the action of the drug is apt to affect the fibres unequally, so that we may have a sharp normal twitch preceding the prolonged contraction (Fig. 64). If the muscle be excited immediately after the prolonged contraction has passed away, it responds with a single twitch like a normal muscle, but if allowed to rest a few minutes, stimulation is again followed by the peculiar long drawn out contraction.

FIG. 63.



A. Tracing of the contraction of a frog's sartorius, poisoned with veratrin, in response to a momentary stimulus. The time-marking indicates seconds.
B Tetanic contraction of normal sartorius in response to rapidly interrupted stimuli. (The duration of the stimulus is indicated by the words 'on' and 'off') It will be noticed that the two curves are practically identical. (Miss Buchanan.)

FIG. 64



Tracing of the contraction of a muscle poisoned by the injection of a strong solution of veratrin, showing the double contraction due to unequal poisoning of different fibres (Biedermann)

The action of sodium salts on muscle is of considerable interest. We are accustomed to use a 0·6 per cent. solution of NaCl as a 'normal fluid' to keep muscle preparations moist. If however the solution be made with distilled water, it has a distinctly excitatory effect upon the muscle, so that single induction shocks may cause tetaniform contractions. The same excitatory effect is still better marked with solutions of Na_2CO_3 (Fig. 65). If a thin muscle, such as a frog's sartorius, be immersed in a solution containing 0·5 per cent. NaCl, 0·2 per cent. Na_2HPO_4, and 0·04 per cent. Na_2CO_3 (Biedermann's fluid), the muscle enters into a series of frequent contractions, so that it may wriggle from side to side, or may even 'beat' for a time with the regularity of heart muscle, though at a much greater rate.

This excitatory action of sodium salts is neutralised by the addition of traces of calcium salts. Hence the normal saline used in the laboratory should always be made with tap water, containing calcium salts.

Potassium salts, although forming so important a constituent of the ash of muscle, act as muscle poisons, quickly and permanently destroying its irritability. If a muscle be transfused with normal fluids containing minute traces of potassium salts, it at once shows all the signs of fatigue, signs which may be removed by washing out the potassium salts by means of 0 6 per cent. NaCl solution. It is possible that the setting free of potassium salts may be one of the factors involved in the development of the normal fatigue of muscle.

SECTION 8

VOLUNTARY CONTRACTION

In the light of our knowledge gained chiefly by electrical excitation of muscles, we have now to inquire into the nature of ordinary voluntary contraction as it occurs in the muscles in the body.

The fact that it is difficult to get an artificial prolonged contraction in excised muscles except by repeated stimulation—that is, by summation of single twitches to form a tetanus—has led us to view almost every voluntary contraction as a tetanus. What further evidence is there for this view?

Muscle-sound.—If we place the end of a stethoscope over the biceps muscle, and listen while we voluntarily contract the muscle, a low sound is heard. This is the muscle-sound, and invariably accompanies any voluntary contraction. Its tone corresponds to about thirty-six vibrations a second, and it was thought to be the first overtone of a note of eighteen vibrations per second, which therefore was looked upon as the rhythm of 'voluntary tetanus.'

But one hears exactly the same note when listening to any irregular sound of low intensity. The roar of London that we hear in the middle of Hyde Park has the same pitch as the muscle-sound of our contracting biceps. And really this muscle-sound proves nothing about the number of contractions composing voluntary tetanus, for it is the natural resonance-tone of the ear, and therefore selected and intensified in the ear when we listen to any irregular mixture of tones and noises.

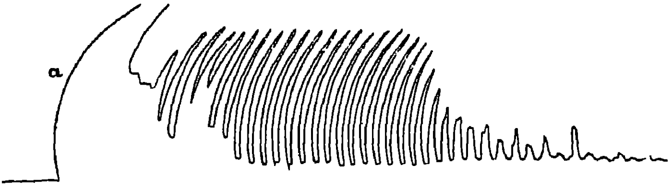
Tracings of most voluntary contractions show superficial vibrations of eight to twelve a second, and this rhythm is seen in many movements, such as the clonic convulsions of epilepsy, and some diseases of the spinal cord. This irregularity would quite well account for the muscle-sound.

But we can get tracings of natural contractions showing eight or ten complete twitches in the second (contraction and relaxation), or a continued contraction with eight or ten superficial waves.

So it is not sufficient to say that voluntary contraction is a tetanus of eight or twelve per second. If it is a tetanus, there must be some means by which each individual contraction can be shortened till it is distinct, or lengthened till it fuses with the next contraction to produce an unbroken tetanus. And we must remember that the electrical stimulus differs in many of its effects from the natural stimulus, and so not transfer all our results of electrical stimulation too unreservedly to the contraction of muscles in the living body in response to the will.

We have in fact definite evidence that discontinuity is not essential for the production of prolonged contraction. Thus we have already seen that, during the passage of a constant current through muscle, there is a continuous contraction in the neighbourhood of the kathode. If the irritability of the muscle at this point be increased by the application of a solution of sodium carbonate, this excitation is propagated to the rest of the muscle and we get a prolonged contraction on closure of the current, followed by rhythmic contractions (Fig. 65).

FIG. 65.

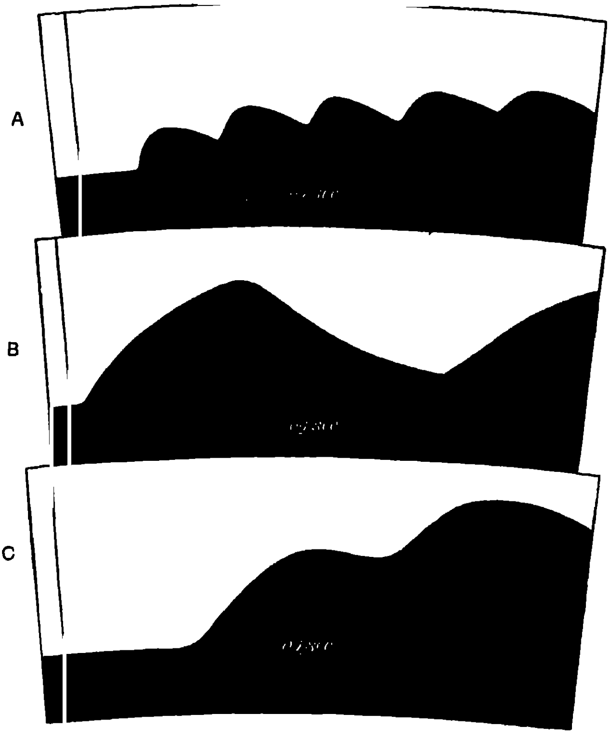


Continued contraction followed by rhythmic contractions of a muscle in response to a constant stimulus (Biedermann) The muscle was excited by the passage of a constant current, the kathodal end having been moistened with a weak solution of Na_2CO_3.

Moreover in excitable frogs (frogs which have been kept at about 2° or 3° C. for some days) the *closure* of a *descending* current through the nerve causes continued contraction of the muscle, and in the same way there may be a prolonged contraction at the *opening* of an *ascending* current through the nerve.

Attempts have been made to decide the question by recording the electrical changes accompanying the natural contractions of a muscle, *i.e.* those excited reflexly through the central nervous system. It was long ago shown by Lovén that a certain discontinuity could be seen in records of such changes, as of the mechanical changes; but a renewed investigation of the subject by Burdon-Sanderson

FIG 66



Electrometer records of the electrical variations of frog's muscle under different conditions (Burdon-Sanderson). A, excited by induction-shocks 14 times per second; B, excited for periods of $\frac{1}{5}$ sec by rapidly repeated induction-shocks (60 per second) alternating with equal periods of rest; C, strychnine spasm ('natural' contraction)

has proved conclusively that this discontinuity is so to speak an accident, and an expression of the tendency of the spinal cord to rhythmic activity. If the electrical changes of a strychnine spasm be photographed by means of the capillary electrometer, it will be seen that each individual spasm or twitch is not a simple muscle twitch, but a prolonged contraction similar to a short tetanus. This is well shown in the accompanying photographs (Fig. 66, c) The period elapsing between the beginning and the culminating point of the electrical change of a single twitch is about $\frac{8}{1000}$ of a second (Figs. 59 and 66, A). In the spasms making up the reflex (natural) contraction, the duration of the electrical change is more than $\frac{50}{1000}$ of a second (Fig. 66, c). The second photograph (Fig. 66, B) shows how we may imitate such a series of changes, not by a series of single stimuli, but by *tetanising* for a succession of periods of 0·2 second alternated with equal periods of rest.

It seems therefore highly probable that the normal reflex or voluntary contraction is not a tetanus (a condition which is a product of the physiological laboratory), but a prolonged single contraction caused by a constant stimulus arriving at the muscle from the central nervous system.

SECTION 9

OTHER FORMS OF CONTRACTILE TISSUE

SMOOTH OR UNSTRIATED MUSCLE

The little we know about the physiology of unstriated muscle is derived chiefly from experiments on the intestine, ureter, bladder, and retractor penis.[1] This tissue differs from voluntary muscle in containing numerous plexuses of nerve-fibres (non-medullated) and ganglion-cells, so that in all our researches it is difficult to be certain whether the results are due to the muscle-fibres themselves, or to the nerves and nerve-cells which are so intimately connected with them; especially as we have as yet no convenient drug like curare, by aid of which we might discriminate between action on muscle and action on nerve.

The differences between unstriated and voluntary muscle, although at first sight very pronounced, on further investigation prove to be in most cases differences of degree only; qualities and reactions which are marked in involuntary muscle being also present in a minor degree in the more highly differentiated tissue.

The contraction of smooth muscle is so sluggish that the various stages of latent period, shortening, and relaxation can be easily followed with the eye. The latent period may be from 0·2 to 0·8 second, and the contraction may last from half to three minutes.

In consequence of this lack of differentiation, the smooth muscle preserves many of the properties of undifferentiated protoplasm, especially an automatic power of contraction, which is regulated by the condition of the muscle. Thus whereas the voluntary muscle is intimately dependent on its connection with the central nervous system, and in the absence of this is reduced to a flabby inert tissue, the smooth muscle isolated from all its nervous connections presents in many cases rhythmic contractions, and can carry out a peripheral adaptation to its environment.

---

[1] The retractor penis, which is found in the dog, cat, horse, hedgehog (but not in rabbit or man), is a thin band of longitudinally arranged unstriated muscle, which is inserted at the attachment of the prepuce, and is continued backwards in a sheath of connective tissue to the bulb, where it divides into two slips which pass on either side of the anus It is innervated from two sources, the *motor* fibres being derived from the lumbar sympathetic and running to the muscle in the internal pudic nerve, while the inhibitory fibres run in the pelvic visceral nerves (nervi erigentes) and are derived from the second and third sacral nerve-roots.

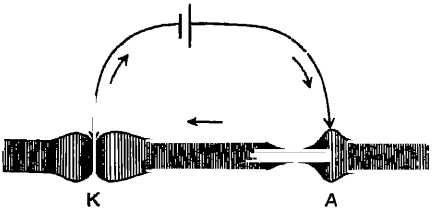
These rhythmic contractions are almost invariably observed if the muscular tissue be subjected to a certain amount of tension, after separation fròm the central nervous system. The rhythm of the contractions may vary from one (spleen) to twelve (small intestine) contractions in the minute.

The stimuli for smooth muscle are essentially the same as for striated. As we should expect however from the sluggish response of this kind of contractile tissue, the optimum rate of change of current which excites is very much slower than in the case of striated muscle. Thus in many instances a single induction shock, even if very strong, is powerless to excite contraction, and the make-induction shock of long duration and low intensity is always more efficacious than the short sharp break-induction current. A still better stimulus is the make or break of a constant current. When the latter form of stimulation is used, response occurs at the make sooner than at the break, and, just as in voluntary muscle, the make excitation starts from the kathode and the break excitation from the anode.

An apparent exception to this statement is afforded by the behaviour of certain forms of involuntary muscle. In the intestine, in the skin of worms, and in many other muscular tubes, the smooth muscle-fibres are arranged in two definite sheets, one consisting of longitudinal, the other of circular fibres If non-polarisable electrodes, connected with a constant source of current, be applied to the surface of the small intestine, when the current is made there will be apparently a strong contraction of the circular coat at the anode, which spreads up and down the intestine, and a linear contraction of the longitudinal coat at the kathode The same result is observed in the earthworm and leech But careful observation shows in each case that the irregularity is really only apparent, and that in the immediate neighbourhood of the anode there is relaxation of both coats, with a contraction of the circular coat on each side, and that at the kathode there is a contraction of both coats The accompanying diagram (Fig 67) will serve to show the condition of the circular coat at each electrode

As a matter of fact, in consequence of the arrangement of the fibres, we have in the neighbourhood of the anode a number of places (virtual kathodes) where the current is *leaving* the muscle cells to enter inert conducting tissues, and in the same way there will be in the neighbourhood of the kathode a number of virtual anodes. Thus if we take the ureter and lead a current through it while it is slung up in thread loops serving as electrodes, there is contraction of both coats at the kathode and relaxation of both at the anode If however the ureter be packed in a pulp of blotting paper moistened with normal saline, thus allowing the current to leave the contractile tissues anywhere along the ureter, we get the same aberrant results of stimulation as are obtained with the intestine.

Fig 67



At the kathode K there is a small line of constriction, surrounded by an area of relaxation At the anode itself the muscle is relaxed, but is strongly contracted on each side of the anode, so that on rough observation it would be thought that contraction occurred at the anode itself.

Summation

We have already seen that if two stimuli be sent into a voluntary muscle within a short interval of time, there is a summation of effect, the contraction due to the second stimulus being piled so to speak on the top of the first contraction. That a maximal twitch is not as high as a tetanus, the product of summation of many twitches, is due to the

Fig 68

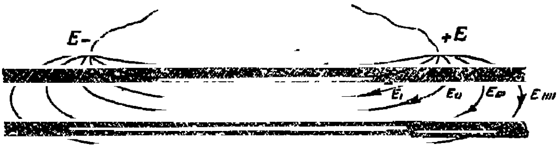
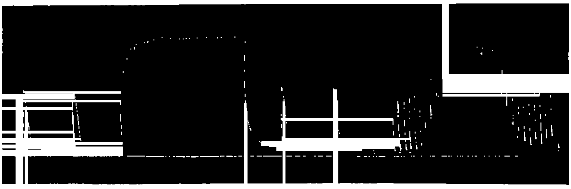


Diagram to show the spread of current which occurs when a current is led through a tube such as the ureter by means of two electrodes applied to its surface It will be noticed that while + E is the anode, there are immediately below and around it a number of kathodes $E_{,}$, $E_{,,}$, $E_{,,,}$, $E_{,,,,}$, due to the current leaving the muscle to flow through indifferent tissues (Biedermann) fact that the relaxation processes of a muscle begin before it has time to overcome the inertia of the mass moved, and so accomplish its maximum shortening. If therefore we support the muscle in any way, whether by screwing up the lever (after-loading) or by sending in a previous stimulus, the contraction due to a stimulus will be more pronounced, until the shortening of the muscle attains that observed in tetanus. For the same reason the height of a single twitch in relation to a tetanus of the same muscle increases as we *slow* the contraction, until, with a prolongation such as is produced by veratrin, there is no difference at all between the height of a maximal single contraction and the height of a tetanus (Fig. 68, p. 143).

FIG 69.



Contractions of a frog's muscle Two single twitches are followed by a tetanus, which is almost twice as high as a single contraction After two more single twitches, the drum was made to rotate more slowly, and single shocks employed, at the same time as the 'after-loading' was continually increased It can be seen that the curve obtained in this way is as high as the original tetanus (v Frey)

These considerations would lead us to expect no trace of any process analogous to summation of contraction in the slowly moving smooth muscle. In the heart muscle this is the case, no increase in the height of a contraction being produced by sending in one, two, or more shocks in quick succession. When however we record the contractions of a muscle, such as the retractor penis, which is more closely under the control of the nervous system, and excite with a series of induction shocks, we get results which at first sight are exactly analogous to the summation of contraction in a voluntary muscle. It may be noticed however that the first three or four stimuli are ineffective, and that there is in this case a summation *before* any contraction has occurred, a *summation of stimuli*. Each stimulus in fact alters the state of the contractile tissue and makes it more ready to respond to the next stimulus, so that the stimuli become more and more effective. If time is allowed for the muscle to relax between successive stimuli, this summation is evidenced by a continually increasing height of contraction, the so-called 'staircase.' It will be remembered that the same initial increase of effect was observed when voluntary muscle was excited by continually recurring stimuli (*v.* Fig. 62, p. 141).

We shall meet with other examples of this summation of stimuli when dealing with the physiology of the central nervous system. It is indeed a fundamental phenomenon in the physiology of excitation.

Chemical Stimulation

Strong salt solution excites contractions just as in the case of skeletal muscle. Many drugs such as physostigmin, ergot, lead salts, digitalis, may act directly on smooth muscle and cause contraction. As one would expect however from the greater independence of the smooth muscle, the action of these drugs varies from organ to organ, muscle-fibres, which apparently are histologically identical, reacting diversely according to their origin.

Mechanical Stimulation

Smooth muscle may react to a local pinch or blow with a local or a general (propagated) contraction. The most important form of mechanical stimulation is that produced by tension. The effect of increasing the tension on smooth muscle may be twofold: causing in the first place relaxation and in the second excitation with increased contraction. These two effects may be illustrated by taking the case of the bladder. If this viscus (which is surrounded by a complete coat of smooth muscle) has all its connections with the central nervous system severed, it is when empty in a state of tonic contraction. If fluid be injected into it rapidly there is a great rise of pressure in its cavity, due to the forcible distension. If however the fluid be injected slowly the bladder muscle relaxes to make room for it, so that a considerable amount of fluid may be accommodated in the bladder without any great rise of pressure. This process of relaxation has however its limit. If the injection of fluid be continued, the walls begin to be stretched passively, and this increased tension acts as a stimulus causing marked rhythmic contractions of the whole bladder.

In the same way the response of a smooth muscle to an electrical stimulus is much increased by previous increase of the tension on the muscle-fibres.

Propagation of the Excitatory State, or Wave of Contraction

In the case of voluntary muscle we have seen that, on stimulating any part of a muscle-fibre, a wave of contraction is started which travels to each end of the fibre, but no further. There is no propagation from muscle-fibre to muscle-fibre, the synchronous contraction of the whole muscle being brought about by simultaneous excitation of all its fibres. This isolation of the excitatory state is not found in smooth muscle. A stimulus applied to any part of a sheet of smooth fibres may travel all over the sheet just as if it were a single fibre. It seems probable indeed that there is protoplasmic continuity by means of fine bridge-like processes between adjacent muscle-cells. And even in the absence of such bridges, the propagation of the contraction could be easily accounted for. Although in the case of voluntary muscle the rule is isolated contraction, yet a very small change in the muscle, such as is produced by partial drying or by pressure, is sufficient to cause the contraction to spread from one fibre to another. Indeed by clamping two curarised sartorius muscles together, as in the diagram (Fig. 70), it is found that stimulation of the muscle A causes contraction of the muscle B. The current of action of A in this case has served to excite a contraction in B.

FIG 70

It must be remembered that in all unstriated muscle the fibres are surrounded by a network of non-medullated nerve-fibres. Some physiologists are inclined to ascribe to these fibres an important part in the propagation of the contraction wave In the case of the heart muscle however, it can be shown almost conclusively that the propagation takes place independently of nerve-fibres, and probably the same is true for certain involuntary muscles

Influence of Temperature

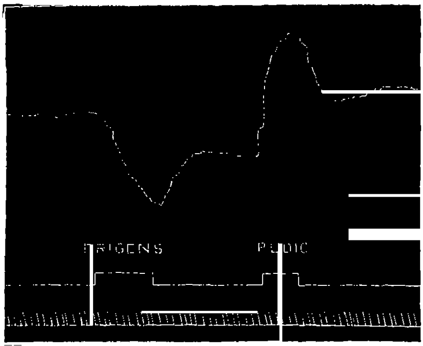
Smooth muscle is extremely susceptible to changes of temperature; we may say as a rule that warming causes relaxation, while application of cold causes a tonic contraction. The condition of the muscle at any given time does not depend only on its actual temperature but also on the rapidity with which this temperature has been reached. Thus a rapid cooling of the retractor penis muscle of a dog from 35° to 25° may cause a contraction as extensive as would be produced by a slow cooling to 5° C. On warming a muscle from 30° to 50° C. it lengthens gradually up to about 40°, and it may then undergo a marked heat contraction (varying in degree in different muscles) at about 50° C. which may pass off at a somewhat higher temperature. It is killed somewhere between 40° and 50° C. It seems very doubtful whether any true rigor mortis occurs in smooth muscle. The hard contracted appearance of the smooth muscle in a recently dead animal is chiefly conditioned by the fall of temperature. On excising the muscle and warming it up again to body temperature, it may again relax and show signs of irritability two or three days after the death of the animal. Different smooth muscles however vary very much in their tenacity of life.

Double Innervation

We have seen that voluntary muscle is absolutely dependent for its activity on the central nervous system. Cut off from this it is flabby and motionless. Its sole function is to contract efficiently and smartly on receipt of impulses arriving along its nerve. It is only necessary therefore that these impulses should be of one character—motor, and we know that each fibre of a muscle, such as the sartorius, receives one efferent nerve-fibre terminating in an end-plate

In the case of smooth muscle however we have a tissue which has an activity and reactive power of its own, and apart from its innervation may be at one time in a state of relaxation, at another in a state of tonic contraction. In order therefore that the central nervous system should have efficient control over such a tissue, it must be able to influence it in *two* directions: it must be able to induce a contraction or increase a contraction already present, and it must also be able to put an end to a spontaneous contraction, *i.e.* to induce relaxation. In order to carry out these two effects, smooth muscle receives nerve-fibres of two kinds from the central nervous system, one kind motor, analogous to the motor nerves of skeletal muscle, the other kind *inhibitory*, causing relaxation or cessation of a previous contraction. All these fibres belong to the visceral or 'autonomic' system. They are connected with ganglion-cells in their course outside the central nervous system, and their ultimate ramifications in the muscle are always non-medullated. A typical tracing of the opposite effects of these two sets of nerves is given in Fig. 71.

FIG 71



Tracing from the *retractor penis* muscle of the dog, showing lengthening (inhibition) on stimulation of the nervus erigens, and a smart contraction on stimulating the pudic (motor) nerve (Movements of muscle reduced ½)

In the invertebrata many 'voluntary' striated muscles probably possess a double innervation Thus in the crayfish, the adductor muscle of the claw consists of striated muscular fibres, every fibre of which is supplied with two kinds of nerve-fibres By exciting these fibres one may get, according to the conditions of the experiment, either contraction of a relaxed muscle or relaxation of a tonically contracted muscle (Fig 72)

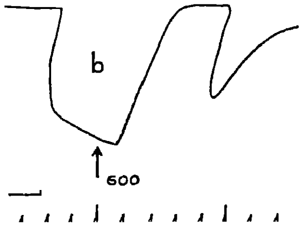
AMŒBOID MOVEMENT

We have already described amœboid movement as seen in the amœba and the white blood-corpuscles. It only remains to enumerate the chief factors that influence its activity.

Amœboid movements can occur only within certain limits of temperature (about 0° C. to 40°); within these limits it is the more active the higher the temperature. At about 45° the cell goes into a condition resembling heat rigor.

The fluid in which the corpuscles are suspended is of great importance. Distilled water, almost all salts, acids and alkalies, if strong enough, stop the action and kill the cell.

FIG 72



Tracing of contraction of adductor muscle of claw of crayfish, showing inhibition resulting from stimulation of its nerve (at *b*) by means of a constant current. The break of the current causes a second smaller inhibition (Biedermann.)

The movements are also stopped by CO_2 or by absence of oxygen.

Artificial excitation, whether electrical, chemical, or thermal, causes universal contraction of the corpuscle, which therefore assumes the spherical form

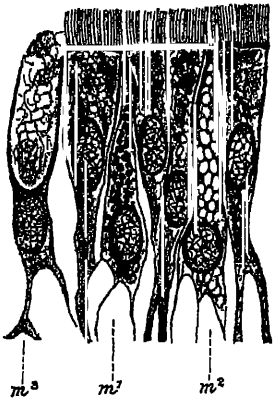
CILIARY MOVEMENT

Cilia are met with in man in nearly the whole of the respiratory passages and the cavities opening into them, in the generative organs, in the uterus and Fallopian tubes of the female, and the epididymis of the male, and on the ependyma of the central canal of the spinal cord and its continuation into the cerebral ventricles.

The cilia (Fig. 73) are delicate tapering filaments which project from the hyaline border of the epithelial cells. There are about twenty or thirty to each cell. The hyaline border is really made up of the enlarged basal portions of the cilia.

In action the cilia bend suddenly down into a hook or sickle form, and then return more slowly to the erect position. This movement is repeated many (twelve to twenty) times a second, and thus serves to move forward mucus, dust, or an ovum, as the case may be. The movement seems to be entirely automatic, and it is quite unaffected by nerves, at any rate in all the higher animals.

Fig. 73.



Ciliated columnar epithelium from the trachea of a rabbit, m^1, m^2, m^3, mucus-secreting cells (Schafer.)

There is however a functional connection between all the cells of a ciliated epithelial surface, so that movement of the cilia, started in one cell, spreads forward as a wave, just as, when the wind blows, waves of bending pass over a field of corn.

The conditions of ciliary action are exactly the same as those for amœboid movement of naked cells.

The minuteness of the object has, up to now, prevented us from deciding whether the cilium is itself actively contractile, or whether it is simply passively moved by the action of the basal part situated in the hyaline border of the cell.

CHAPTER V

NERVE-FIBRES (CONDUCTING TISSUES)

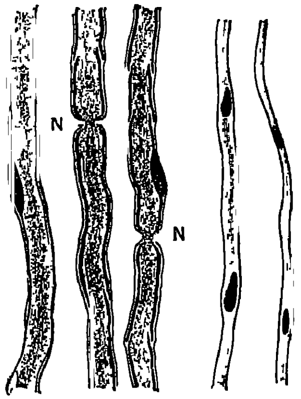
SECTION 1

GENERAL PROPERTIES OF NERVE-FIBRES

IN the last chapter we studied incidentally some of the functions of nerve-fibres. We found that, when we stimulated the nerve of a nerve-muscle preparation at any part by electrical, thermal, or mechanical means, the stimulus was followed, after a very short interval, by a contraction of the muscle. This observation illustrates the two functions of nerve-fibres, irritability and conductivity,—that is to say, a suitable stimulus can set up changes in any part of the nerve, which are transmitted down the nerve without any visible effects occurring in it; and it is not until this nervous change has reached the muscle that a visible effect takes place in the shape of a contraction. Now in the human body a direct excitation of the nerve-fibre in its course never takes place under normal circumstances. The only function the nerve-fibre has to perform is that of conducting impulses from the sense organs at the periphery to the central nervous system, and efferent impulses from this to the muscles and others of its servants. Hence it is absolutely essential that there should be vital continuity along the whole length of the fibre. Damage to any part of it, such as by crushing, heat, or any other injurious condition, infallibly causes a block to any impulse.

It was pointed out in the introductory chapter that a nerve-fibre is essentially a long process or arm of a nerve-cell. The cells may either be situated on the surface of the body or, as in most cases in the higher animals, they may be withdrawn from the surface to form special collections of cells such as the posterior root ganglia, or a whole mass of cells and interlacing processes making up a central nervous system. Although all nerves are alike in possessing as their conducting part the continuous strand of protoplasm produced from the nerve-cell, they develop in the course of growth certain histological differences, which appear to bear some relation to the nature of the processes they conduct or to the character of their parent-cell. Thus all the fibres which are given off from and which enter the central nervous system, *i.e.* the brain and spinal cord, belong to the class known as medullated. In this type the conducting core or axis-cylinder is surrounded with a layer of apparently insulating material known as myelin, forming the medullary sheath, or the sheath of Schwann. This sheath consists of a fatty material composed largely of lecithin, and staining black with osmic acid, supported apparently in the interstices of a network formed of a horny substance known as neurokeratin. The medullary sheath is surrounded by a structureless membrane, the primitive sheath or neurilemma. At regular intervals a break occurs in the medullary sheath, the neurilemma coming in close contact with the axis-cylinder. This break is the node of Ranvier, the intervening portions of medullated nerve being the internodes. In each internode, lying closely under the neurilemma, is an oval nucleus embedded in a little granular protoplasm. The medullated nerve-fibres vary considerably

FIG 74.



Three medullated and two non-medullated nerve-fibres, N, node of Ranvier (from Yeo) in diameter, the largest fibres being distributed to the muscles and skin, the smallest carrying impulses from the central nervous system to the viscera. The latter class all come to an end in some collection of ganglion cells of the sympathetic chain or peripheral ganglia, the impulses being carried on to their destination by a fresh relay of non-medullated nerve-fibres.

The non-medullated fibres differ from the medullated simply in the absence of a medullary sheath. They possess, in many cases at any rate, a primitive sheath, under which we find nuclei lying closely on the side of the fibre and bulging out the sheath. In their ultimate ramifications they tend to form close networks or plexuses and appear to lose the last traces of a sheath.

The medullated nerves are bound together by connective tissue (endoneurium) into small bundles, which are again united by tougher connective tissue into larger nerve-trunks. These fibres as a rule branch only when in close proximity to their destination, and then the branching always occurs at a node of Ranvier.

SECTION 2

PROPAGATION ALONG NERVE-FIBRES

The velocity of propagation along a nerve-fibre may be measured, although in early times it was thought to be as instantaneous as the lightning flash. To measure the velocity of propagation in a motor nerve, a frog's gastrocnemius is prepared, with a long piece of sciatic nerve attached. The muscle is arranged (Fig. 75) so that its contraction may be recorded on a rapidly moving surface, on which are also recorded, by means of electro-magnetic signals, the moment at which the stimulus is sent into the nerve, and also a time-marking showing $\frac{1}{350}$ sec. Tracings are now taken of the contraction of the muscle: first, when the nerve is stimulated at its extreme upper end, secondly, as close as possible to the muscle. It will be found that the latent period, which elapses between the point at which the stimulus is sent into the nerve and the point at which the lever begins to rise, is rather longer in the first case than in the second. The difference in the two latent periods gives the time that it has

FIG 75

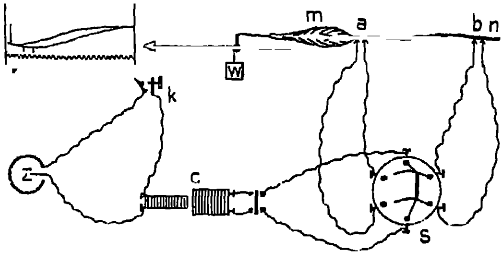


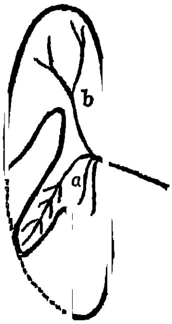
Diagram of arrangement of experiment for the determination of the velocity of transmission of a motor impulse down a nerve The battery current passes through the primary coil of the inductorium *C*, and a 'kick over' key *k* By means of the switch *S*, the break shock in the secondary circuit can be sent through the nerve *n*, either at *b*, or at *a* The muscle *m* is arranged to write on the blackened surface of a trigger or pendulum myograph, and is excited during the passage of the recording surface by the automatic opening of the key *k* (The time-marker is not shown) taken for the nervous impulse to travel down the length of nerve between the two stimulated points. Calculated in this way, the velocity of propagation in frog's nerve is about 28 metres per second.

The velocity of propagation in sensory nerves is more difficult to determine, owing to the fact that a sensory impulse, on arrival at the receiving organ—*i.e.* some part of the central nervous system—does not at once give rise to some definite recordable mechanical change, such as a muscular contraction. There is another method of determining the velocity of conduction, which may be used also with sensory fibres. The passage of a nerve-impulse down a nerve, just as the passage of a wave of contraction along a muscle-fibre, is immediately preceded or accompanied by an electrical change, which also travels along the nerve as a wave of 'negativity.' The velocity of propagation of this wave may be measured, and is found to give the same numbers as the velocity determined by the preceding method.

The existence of this electrical change enables us to show that a nerve-impulse, excited at any point in the course of a nerve-fibre, travels *in both directions* along the fibre. The power of nerves to transmit impulses in either direction is shown further by the experiment known as Kuhne's gracilis experiment. The gracilis muscle of the frog is separated into two portions by a tendinous intersection, so that there is no muscular continuity between the two halves. The nerve to the muscle divides into two branches, one to each half, and at the point of junction *there is division of the axis-cylinders themselves.* It is found that if the section *a* in the diagram (Fig. 76), which is quite isolated from the rest of the muscle, be stimulated, as by snipping it with scissors, the whole muscle contracts. If however the portion of the muscle which is free from nerve-fibres be stimulated in the same way, the contraction is limited to the fibres directly stimulated, showing that in the first case the stimulus excited nerve-fibres which transmitted the impulse *up* the nerve to the point of division and then *down* again to the other half of the muscle. Since nerves have this power of conduction in both directions, it might be thought that a single set of nerve-fibres might very well subserve both afferent and efferent functions, at one time conducting sensory impulses from periphery to cord, at another time motor impulses from cord to muscles. But this is not the case. As a matter of fact we find in the body a marked differentiation of function between various nerve-fibres.

We have already mentioned the division of nerves into afferent and efferent, and we find further that each of these afferent or efferent fibres has its own proper impulses to conduct, and conducts only these impulses. Thus some fibres in the anterior spinal roots conduct ordinary motor impulses to muscles, others impulses causing contraction or relaxation of the muscular walls of arteries, or which quicken or slow the contractions of the heart. We shall return to this question of restricted function of nerve-fibres under the heading of 'Muller's law of specific irritability' when we come to treat of the special senses.

FIG 76.



Kuhne's gracilis experiment

The rate of propagation of a nervous impulse is quickened by heat (up to about 38° C.) and slowed by cold. At a little over 0° C. the rate in frog's nerve is only about one metre per second.

Events accompanying the Passage of a Nervous Impulse

In muscle we saw that the passage of an excitatory wave was accompanied or followed by electrical changes, production of heat, and mechanical change, all pointing to an evolution of energy from the explosive breaking down of contractile material.

In nerve however, which serves merely as a conducting medium, we should not expect so much expenditure of energy, or in fact any expenditure at all. All that is necessary is that each section of the nerve should transmit to the next section just so much kinetic energy as it has received from the section above it. And experiment bears out this conclusion. The most refined methods have failed to detect the slightest development of heat in a nerve during the passage of an excitatory process; and we know already that there is no mechanical change in the nerve. The only physical change in a nerve under these circumstances is the development of a current of action. A nerve becomes, when excited at any point, negative at this point to all other parts of the nerve, and, just as in muscle, this 'negativity' is propagated in the form of a wave in both directions along the nerve.

That the excitatory process in nerves is probably accompanied by certain small chemical changes is indicated by the facts that, in the complete absence of oxygen, the nerve fibres lose their irritability, and that this loss of irritability is hastened by repeated stimulation of the nerve. When the irritability has been abolished by stimulation in the absence of oxygen, it may be restored within a few minutes by re-administration of oxygen to the nerve.

If we connect a galvanometer to two points of an uninjured nerve, no current is observed, all points of a living nerve at rest being iso-electric. On making a cross-section of the nerve at one leading-off point, a current is at once set up, which passes from the surface through the galvanometer to the cross-section. This is a demarcation current, set up at the junction between living and dying nerve. It will be noticed that this current rapidly diminishes in strength and finally disappears, owing partly to the fact that the dying process started in the nerve by the section extends only as far as the next node of Ranvier and there ceases, so that after a short time the electrode applied to the cross-section is simply leading off an intact living axis-cylinder through the dead portion of the nerve, which acts as an ordinary moist conductor. On making a fresh section just above the previous one, the process of dying is again set up, and the demarcation current is restored to its original strength. If, while the demarcation current is at its height, we stimulate the other end of the nerve with an interrupted current, the needle of the galvanometer swings back towards zero, *i.e.* there is a negative variation of the resting current.

In order to demonstrate the wave-like progression of the electrical change from the excited spot along the nerve, it is necessary, as in the case of muscle, to make use of the repeating rheotome or of a very sensitive capillary electrometer. It is then found that the change progresses along the nerve at the same rate as the nervous impulse, *i.e.* twenty-eight to thirty-three metres per second. But it lasts only an extremely short interval of time at each spot, viz. six to eight ten-thousandths of a second. Thus the length of the excitatory wave in nerve is about 18 mm.

SECTION 3

EXCITATION OF NERVES

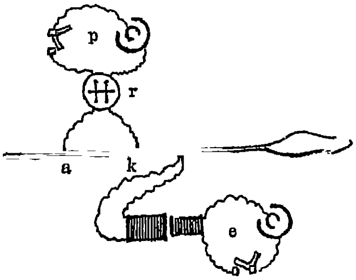
We must now study more fully the changes which take place in a nerve during the passage of a current through it, and the manner in which these changes are able to generate a nervous impulse. Under normal circumstances, if a constant current be passed through the nerve of a nerve-muscle preparation for a short time, the muscle responds only at the make and the break of the current, remaining perfectly quiescent all the time the current is passing. If the nerve be in a very excitable condition, it is possible that the muscle may be thrown into a tetanus or continued contraction during the whole time that the current is passing (closing tetanus). On the other hand, if a strong ascending current be passed through the nerve for a considerable time, the muscle when the current is broken may go into continued contraction, which may last some time. Normally however the muscle simply responds with a single twitch at the make and break of the current; although, on investigating the condition of the nerve *during* the passage of the current, we find that it is considerably modified.

This modification in the condition of the nerve is spoken of as *electrotonus*, and includes changes in its irritability and its electrical condition.

To investigate these changes the following apparatus is necessary:—two constant batteries, induction coil, a reverser and keys, a pair of non-polarisable electrodes, and a pair of ordinary platinum electrodes. Fig. 77 represents roughly the arrangement of the experiment. A constant current from the battery is led through a part of the nerve by means of non-polarisable electrodes, which are about one inch apart. In this circuit we put a reverser, by means of which the direction of the current of the nerve may be changed at will, and a key to make or break the current. This is the polarising circuit. The other battery is arranged in the primary circuit of the coil, a key being interposed, so that we may use make or break induction-shocks, which are applied to the nerve by means of the small platinum electrodes. The tendon of the muscle is connected by a thread with a lever, which is arranged to write on a smoked surface, so that the height of the contraction can be recorded.

We first find the position of the secondary coil, at which the break induction-shock is a submaximal stimulus, and we employ this strength of stimulus throughout the experiment. The make induction-shock is prevented from acting on the nerve by closing a short-circuiting key in the circuit of the secondary coil. The nerve is now stimulated at various points with a single break induction-shock, and the contractions recorded. The heights of these contractions serve to indicate the irritability of the nerve at the point stimulated. We now throw the polarising current into the nerve At the make of this current the muscle will probably respond with a twitch which is not recorded. We then test once more the irritability of different points of the nerve, and we find that, when the stimulus is applied near (a) the point where the current enters the nerve (anode), the stimulus, which before gave a moderately large contraction of the muscle, now has either no effect or else produces a very weak contraction. On the other hand, in the region of the kathode the stimulus, which before was submaximal, has now become maximal, as is shown by the increase in the height of the contraction evoked by the induction-shock.

Fig 77



Arrangement of apparatus for showing electrotonic changes in irritability e. Exciting current p Polarising circuit r Pohl's reverser

We now reverse the direction of the polarising current, so that the current of the nerve runs from (k) to (a). With this reversal of current there is also a reversal of the changes in the nerve; that is to say, the normally submaximal stimulus is maximal when applied near (a), and minimal when applied near (k). On break of the polarising current the condition of the nerve returns to normal, and the submaximal stimulus is once more submaximal throughout.

This return to normal conditions however is not immediate, since the first effect of breaking the current is a swing back, so to speak, past the normal, the diminished irritability at the anode giving place to an increased irritability, which only gradually subsides In the same way, immediately after the polarising current has ceased to flow, the neighbourhood of the kathode acquires a condition of diminished irritability, and this only gradually gives place to a normal condition.

This experiment teaches us that, when a constant current is passed through a nerve, there is increase in the irritability in the nerve near the kathode, and a diminution in irritability near the anode. These conditions of increased and diminished irritability are spoken of as *katelectrotonus* and *anelectrotonus* respectively. In the previous chapter we learnt that a make contraction always starts from the kathode, and a break contraction from the anode. Now the event that takes place at the kathode on make and at the anode on break of a constant current is, as the last experiment shows us, a rise in irritability, in the former case from normal to above normal, in the latter from subnormal to normal. Hence we may say that the excitation is caused by a sudden rise of irritability, which may be due either to a sudden appearance of katelectrotonus, or a sudden disappearance of anelectrotonus. I have said sudden, because the steepness of the rise of irritability is a necessary factor in causing excitation. If the polarising current passing through a nerve be slowly and gradually increased to considerable strength, it will give rise to no contraction. The degree of suddenness of the rise, which is most beneficial in causing contraction, varies with the nature of the tissue stimulated. Thus it is more rapid in nerve than in muscle, and in pale muscle than in red muscle, and in voluntary muscle than in unstriated muscle.

It is evident that there must be, somewhere between the anode and kathode, an indifferent point—that is to say, a region where the irritability is neither increased nor diminished, We find experimentally that this indifferent point is nearer the anode when the polarising current is weak, and gets nearer to the kathode as the current is strengthened, so that with very strong currents nearly the whole intrapolar length is in a condition of anelectrotonus (Fig. 78). When a strong polarising current is used, the depression of irritability at the anode is so marked that no impulse can pass this region Thus if we send a very strong ascending current through the nerve, there is no contraction at make. This is owing to the fact that the impulse started at the kathode on make of the current cannot reach the muscle, its passage down the nerve being blocked in the region of the anode (Fig. 79, A).

FIG 78

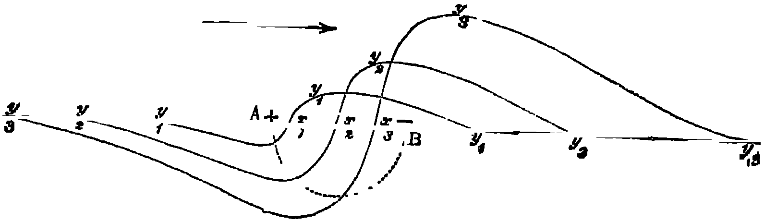


Diagram to show the variations of irritability in a nerve during the passage of polarising currents of different strengths The degree of change is represented by the distance of the curves from the base line, the part of the curve below the line signifying *decrease*, that above the line *increase* of irritability. A, anode; B, kathode, y_1, effect of weak current, y_2, medium current, y_3, strong current It will be noticed that the indifferent point, x, where the curve crosses the horizontal line, approaches nearer and nearer the kathode as the current is increased in strength (from Foster, after Pfluger)

FIG. 79

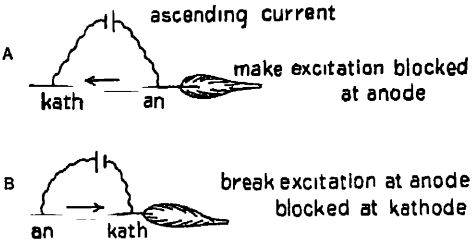

ascending current
A
make excitation blocked at anode
kath
an
B
break excitation at anode blocked at kathode
an
kath

Diagram to show the blocking effect of a strong constant current passed through the nerve of a nerve-muscle preparation

The results of stimulating motor nerves by means of constant currents were studied by Pflüger and, embodied in a table, make up what is known as Pflüger's law. The result of stimulation varies with the strength of a current.

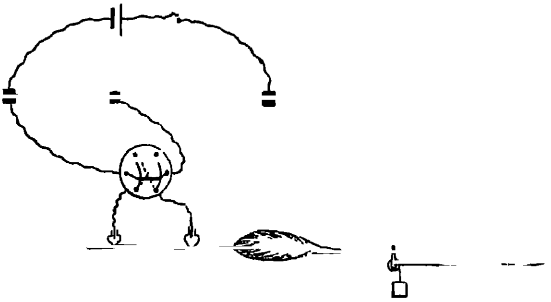
Law of Contraction

Strength of current	Ascending		Descending	
	Make	Break	Make	Break
Weak	c	O	c	O
Medium	c	c	C	c
Strong	O	C or T	C or T	O

c = contraction. C = strong contraction. T = tetanus. O = no effect.

With the weakest currents, excitation occurs only at make, since a make-stimulus, *i.e.* the rise of katelectrotonus, is always more effectual than a break-stimulus, *i.e.* the disappearance of anelectrotonus. With currents of moderate strength, excitation occurs both at make and break, being better marked at make, especially in the case of descending currents. With very strong currents, we get a contraction at make only when the current is descending, since, when the current is ascending, the excitation started at the kathode cannot pass the block at the anode. For the same reason a break contraction is obtained only with an ascending current, since at the break of a descending current there is a swing-back of the nerve at the kathode to a condition of diminished irritability, which effectually blocks the excitation started higher up the nerve at the anode.

Fig. 80.



Arrangement of experiment to demonstrate Pflüger's law of contraction.

The arrangement of the experiment for demonstrating Pflüger's law is shown in Fig. 80. The strength of the current is graduated by means of the rheochord, the current being led into the nerve by means of non-polarisable electrodes. It is extremely important in these experiments to avoid any injury or drying of the nerves at either of the two electrodes, since the excitatory effect either at make or break would be abolished by local injury.

These results, worked out chiefly on motor nerves, have been confirmed as far as possible experimentally on sensory nerves, and on muscle and contractile tissues generally, and probably hold good for all irritable living tissues.

It is said that an anelectrotonus takes some time to attain its full height, and a katelectrotonus reaches its maximum almost directly after the current is made. Hence a current of very short duration probably excites only at the make, the break occurring before the anelectrotonus is developed enough for its disappearance to cause a stimulus. Thus induction-shocks (both make and break) may be looked upon as make-excitations, the excitation however being stronger in the case of the break induction-shock than in that of the make.

Other things being equal, a current of given strength causes a stronger excitation the greater the length of nerve that it flows through. It must be remembered however that the nerve offers considerable resistance to the passage of the current, and so, to keep the current constant while increasing the length of intrapolar nerve, we must largely increase the electromotive force employed.

A very convenient method of showing the effect of the length of intrapolar nerve on excitation has been suggested by Gotch. The two sciatic nerves of a frog are dissected out, one of them being in connection with the gastrocnemius These are first arranged as in Fig 81 A (p 173) *a*, *b*, and *c* are three non-polarisable electrodes, the terminals of a constant battery being connected to *a* and *c*. The position of the rider on the rheochord is then ascertained at which make of the current just excites contraction in the muscle of nerve 2, the current in this case passing from *a* to *b* along nerve 1, and from *b* to *c* along a small piece of nerve 2 We will suppose that eleven units of current are necessary to produce excitation *b* is then withdrawn and the nerve 2 laid on *a* (Fig 81, B), so that the current can now pass from *a* to *c* entirely through a long stretch of nerve 2 On again seeking the minimal stimulus, it will be found that a smaller current is sufficient to excite, contraction being obtained with seven units Since the length of nerve traversed, and therefore the resistance to the current, are the same in both cases, it is evident that a current is more effective the greater the length of excited nerve that it traverses

A nerve cannot be excited by currents passed transversely across it, since in such cases the anode and kathode lie so close to one another in a nerve-fibril, as it is traversed by a current, that their effects counteract one another.

Electrical Stimuli as applied to Human Nerves

When we attempt to apply the results gained on frog's nerves to man, we are met at once by the difficulty that we cannot dissect out the nerves and apply stimuli to them directly. So usually unipolar excitation is used, one electrode, either anode or kathode, being applied to the nerve to be stimulated, and the other to some indifferent point, such as the back. It is evident under these circumstances that the current is concentrated as it leaves the anode and reaches the kathode, and diffuses widely in the body, seeking the lines of least resistance. Thus it is impossible to get pure anodic or kathodic effects. If the anode be applied over the nerve, the current enters by a series of points (the polar zone), and leaves by a second series (the peripolar zone). The polar zone will thus be in the condition of anelectrotonus, and the peripolar zone in that of katelectrotonus. The current however will be more concentrated at the polar than at the peripolar zone, and so the former effect will predominate. These restrictions in the

FIG. 81

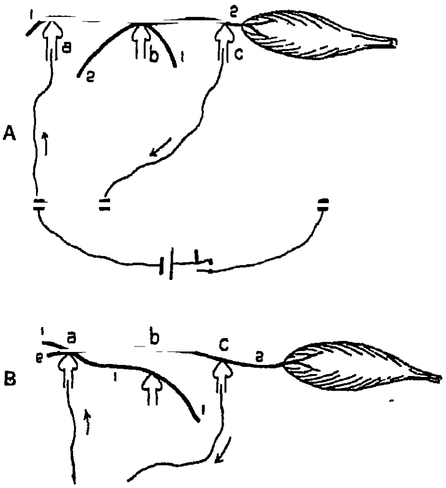


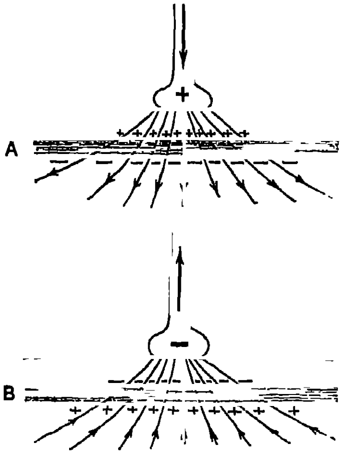
Diagram of arrangement of experiment for investigating the influence of the intrapolar length of nerve on the excitatory effect of the current application of the current cause slight apparent irregularities in the law of contraction as tested on man.

Other Methods of Stimulation

1. *Thermal.* If the temperature of a nerve be gradually raised, no effect is noticed till about 40° C. is reached, when the muscle may enter into weak quivering contractions. Sudden warming of the nerve always gives rise to excitation. At about 45° C. the nerve loses its irritability and dies.

A nerve may be rapidly cooled without any excitation taking place. At about 0° C. the conductivity of mammalian nerve-fibres is absolutely abolished, and hence this method of cooling is of great value when it is required to divide a nerve physiologically without exciting it.

Fig. 82.



Electrodes applied to the skin over a nerve-trunk In A the polar area is anelectrotonic and the peripolar katelectrotonic The former condition therefore preponderates, since the current here is more concentrated In B the conditions are reversed, the polar zone corresponding in this case to the kathode. (Waller)

2. *Mechanical.* A nerve may be excited by crushing or cutting. These methods however destroy the nerve. It is possible to excite a nerve mechanically, without any serious injury to it, by carefully graduated taps, and this method has been used in investigating the phenomena of electrotonus.

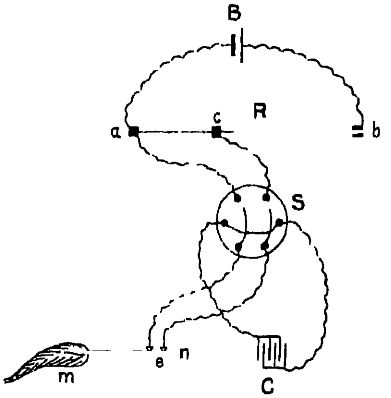
3. *Chemical.* All chemical stimuli applied to the nerve

have a speedy effect in destroying its irritability. The chemical stimuli most used are strong salt solutions, glycerin, or weak acids. If any one of these be applied to a motor nerve, the muscle enters into an irregular tetanus, which lasts till the irritability of the nerve is destroyed at the part stimulated. It is thus evident that we are justified in our choice of electrical stimuli in all ordinary experiments on nerves.

The Energy involved in the Excitation of a Nerve

We have hitherto only considered electrical stimulation by means of a constant current or an induced current It is possible however to store up a certain quantity of electricity in a condenser and then to excite a nerve by discharging the condenser through it[1] The arrangement of such an experiment is shown in Fig. 83 By means of the switch S, the condenser can be put into connection either with the battery from which it receives its charge or with the nerve through which it can discharge By knowing the capacity of the condenser and the electromotive force by which it is charged, we can estimate the energy of the charge sent through the nerve

FIG. 83



Arrangement of apparatus for the excitation of a nerve by means of condenser discharges B, battery, R, rheochord; c, rider of rheochord, S, switch (Pohl's reverser without cross wires); C, condenser, n, nerve; m, muscle, e, non-polarisable electrodes

$$E \text{ (energy in ergs)}[2] = 5\ FV^2$$

(F = capacity in microfarads, V = electromotive force in volts)

---

[1] For explanation of condenser see Appendix.

[2] An erg is the amount of work produced or energy expended by the action of one *dyne* through one centimetre

A dyne is the force which will give to a mass of one gram an acceleration of one centimetre per second per second.

In this way it has been found that the energy of a minimal effective stimulus for frog's nerve is about $\frac{1}{1000}$ of an erg.

From what we have previously said about the relation of the rate of change of current to its excitatory effect, it is evident that the amount of energy necessary to excite the nerve will vary with the rate at which the condenser is allowed to discharge through the nerve This rate can be modified by altering the resistance in the discharging circuit or by altering the electromotive force of the charge, and this method has been adopted by Waller in determining the so called 'characteristic' of nerve, viz. the rate of change at which excitation is obtained with a minimal expenditure of energy.

SECTION 4

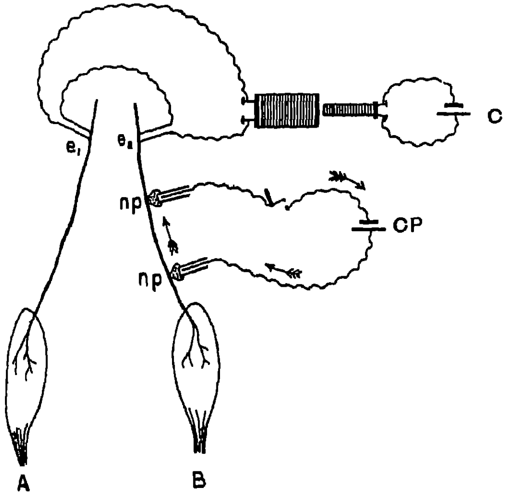
THE CONDITIONS AFFECTING THE ACTIVITY OF NERVE

The Influence of Fatigue

In the description of the phenomena of muscular fatigue given in the last chapter it was assumed that the muscle was being excited directly. The same phenomena are however observed when the muscle is excited through its nerve, though in this case fatigue comes on much more quickly. If, after the muscle has been excited in this way until exhausted, it be excited directly, it will respond with a contraction nearly as high as at the beginning of the experiment. We see therefore that the nervous structures are more susceptible to the influences causing fatigue than the muscle itself, and it can be shown that the weak point in the nerve-muscle preparation is not the nerve, but the end-plates. In fact it is not possible to demonstrate any phenomena of fatigue in the nerve-trunk. This fact can be shown in *mammals* by poisoning the animal with curare, and then stimulating a motor nerve continuously while the animal is kept alive by means of artificial respiration. As the effect of the curare on the end-plates begins to wear off in consequence of its excretion, the muscles supplied by the stimulated nerve enter into tetanus.

The same fact may be shown on the excised nerve-muscle preparation of the frog. The gastrocnemii of the two sides with the sciatic nerves are dissected out, and an exciting circuit is so arranged that the interrupted secondary currents pass through the upper ends of both nerves in series. At the same time a constant cell is connected with two non-polarisable electrodes (*np*, *np*) placed on the nerve of B, so that a current runs in the nerve in an ascending direction. The effect of passing a constant current through a nerve is to block the passage of impulses through the part traversed by the current. When the constant *polarising* current is made, the muscle B may give a single twitch, and then remains quiescent. The exciting current is then sent through both nerves by the electrodes e_1 and e_2. The muscle A enters into tetanus, which gradually subsides owing to 'fatigue.' When A no longer responds to the stimulation, the constant current through the nerve of B is broken. B at once enters into tetanus, which lasts as long as the contraction did in the case of A, and gradually subsides as fatigue comes on. Since both nerves have been excited throughout, it is evident that the fatigue does not affect the nerve-trunk. We have already seen that a muscle will respond well to direct stimulation when stimulation of its nerve is without effect, and must therefore conclude that the first seat of fatigue is the junction of nerve and muscle, *i.e.* the end-plates.

Fig. 84.



Arrangement of experiment for demonstrating the absence of fatigue in medullated nerve-fibres EC, exciting circuit, CP, polarising circuit

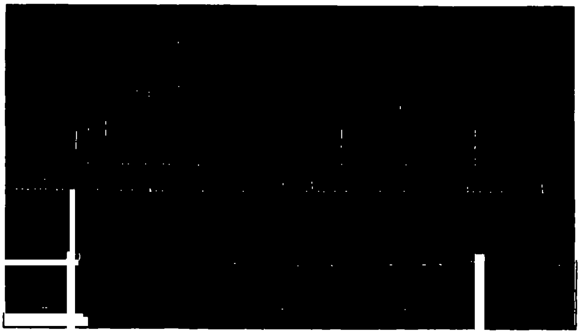
In the normal intact animal, the break in the neuromuscular chain which is the expression of fatigue occurs still higher up, *i.e.* in the central nervous system, and is probably due to some reflex inhibition of the central motor apparatus from the muscle itself. Thus after complete fatigue has been produced in a muscle so far as regards voluntary efforts, direct stimulation of the muscle itself or its nerve will produce a contraction as great as would have been the case at the beginning of the experiment.

The Effect of Injury—The Ritter-Valli Law

The irritability of the nerve of a muscle-nerve preparation is not equal in all parts of its course, but is greater at the upper end, probably in consequence of the proximity of the cross-section.

Some time after a motor nerve is divided, the increased irritability at the upper end gives way to a decreased irritability, and this decrease goes on till the nerve is no longer excitable. The diminution in excitability gradually extends down the nerve-fibre, so that the part of the nerve nearest the muscle remains excitable the longest. This progressive change in the irritability of a nerve after section is spoken of as the Ritter-Valli law. It is soon followed by definite histological changes in the nerve, which we shall describe later on (see Chap. XIV.).

FIG. 85.



Tracing of muscle contractions to show effect of cooling a nerve on its excitability The lower line indicates the changes in temperature of the excited part of the nerve The muscle responded only when the nerve was cooled, the stimulus becoming ineffectual when the nerve was warmed (Gotch).

The Influence of Temperature

The excitability of a nerve is, within certain limits, increased by cooling the nerve, and diminished by raising its temperature (Fig. 85).[1] Thus, if a frog be cooled to 2° or 3° C.

---

[1] This is true for all stimuli except induction-shocks and extremely short galvanic currents (less than 0 005 sec), with which the irritability of nerve is increased by warming and diminished by cooling The same appears to be true for ventricular cardiac muscle, but in the case of voluntary muscle the excitability for *all* forms of stimuli is increased by cooling. (Gotch)

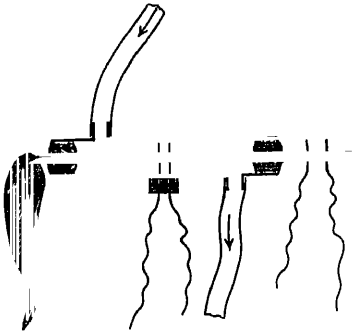
for a day, it will be found that simple section of its sciatic nerve may suffice to send the gastrocnemius into continued contraction, and under these circumstances 'closing tetanus' may be obtained with the greatest ease. The opposite effects of cooling on the conductivity and excitability of nerves show that these properties are possibly independent, and are not affected by the same conditions.

The Influence of Drugs

The most important drugs with an influence on nerve-fibres are those belonging to the class of anæsthetics. Of these we may mention carbon dioxide, ether, chloroform, and alcohol.

The action of any of these substances on the excitability and conductivity of a nerve may be studied by means of the simple apparatus represented in Fig. 86 The nerve of a nerve-muscle preparation is passed through a glass tube which is made air-tight by plugs of normal saline clay surrounding the nerve at the two ends of the tube By means of two lateral tubulures a current of CO_2, or air charged with vapour of ether or other narcotic, can be passed through the tube The nerve is armed with two pairs of electrodes which are stimulated alternately, the pair within the tube serving to test the action of the drug on the *excitability*, while the pair outside the tube shows the presence or absence of any effect on the *conducting power* of the nerve below it

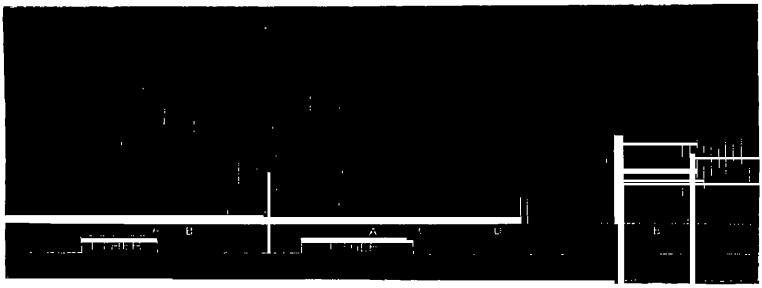
FIG 86.



Of the gases and vapours mentioned above, CO_2 and ether both diminish and finally abolish the excitability and conductivity of the nerve-fibres. The conductivity however persists after all trace of excitability has disappeared, before in its turn being also abolished. On removing the gas or vapour by blowing air over the nerve, the conductivity and excitability gradually return in the reverse order to their disappearance (Fig. 87).

Alcohol is said to increase the excitability or leave it unaffected, while diminishing the conductivity of the nerve.

FIG 87.



Tracing to show the effect of ether on excitability and conductivity of nerve Nerve excited by single induction-shocks alternately within and above ether chamber. The vertical lines indicate contractions of the muscle (gastrocnemius). The lower line indicates the periods during which the nerve was exposed to the action of ether. A, disappearance of *excitability*; B, reappearance of *excitability*; C, disappearance of *conductivity*; D, reappearance of *conductivity*. (From a tracing kindly lent by Prof. Gotch)

Chloroform rapidly abolishes both excitability and conductivity. It is a much more severe poison than the drugs just mentioned, so that in many cases its effects are permanent, and no, or only a very partial, recovery of the nerve is obtained on removal of the chloroform vapour from the apparatus.

SECTION 5

POLARISATION PHENOMENA IN NERVE

Electrotonic current.—In describing the effects of the passage of a constant current through a nerve, we only mentioned alterations of irritability. There are however various other phenomena which are more purely physical in their nature.

If a constant current be passed through a nerve-fibre through the electrodes (x) and (y)—(x) being the anode and (y) the kathode—and the extrapolar portions of the nerve (ab, cd) be connected with galvanometers, it is found that the needles of both are deflected, and the direction of the deflection shows the existence of a current in the extrapolar portions of the nerve (a) to (b), and from (c) to (d).

FIG 88.

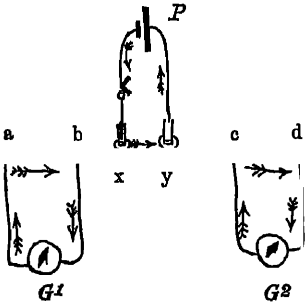
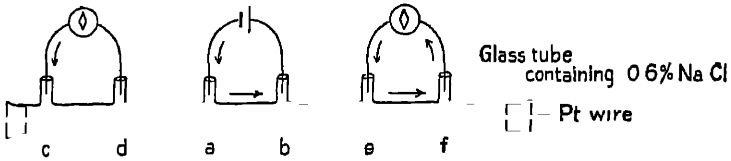


Diagram showing electrotonic currents. P, polarising circuit, G^1 G^2, galvanometers.

The galvanometers will indicate, before the passage of the polarising current, the ordinary demarcation current of the nerve resulting from the cross-section at the upper end. This current flows, in the outer circuit, from equator to cut end, and therefore in the nerve-fibre from (a) to (b), and from (d) to (c) The effect of closing the polarising current will be to increase the current of rest between (a) and (b), and to diminish that between (c) and (d)

We thus see that the passage of a current through a part of a nerve gives rise to a current flowing through a considerable portion of the nerve-fibre on each side of the polarising current and in the same direction. This current is called the electrotonic current. It must not be confounded with the current of action, which originates at one of the poles, only at make or break of the current, and is transmitted thence in the form of a wave with a measurable velocity of about 30 metres per second. The electrotonic current is developed instantaneously, and lasts the whole time that the current is flowing through the nerve. Its production is dependent on the occurrence of polarisation between the sheathing and conducting part of the nerve-fibre and may be exactly reproduced on a model consisting of a core of zinc or platinum wire in a casing of cotton soaked with ordinary salt solution. Although thus physical in origin, its production is dependent on the vitality of the nerve, and so is not to be confounded with the simple spread of current.

FIG. 89.



Apparatus for imitating the polarisation phenomena in medullated nerve ('*Kernleiter*' model).

The polarisation phenomena resulting from the passage of a constant current through a medullated nerve can be studied on a model made up of a glass tube filled with normal salt solution, containing a platinum or zinc wire stretched through it (Fig. 89). On leading a current through *a* and *b*, and connecting *c* and *d* with a galvanometer, a current will be observed in the extrapolar portion of the model in the same direction as in the intrapolar. That this spread of current is due to polarisation is shown by the fact that, if the model be made of zinc wire immersed in saturated zinc sulphate solution, where no polarisation can occur, the spread of current to the extrapolar area is also wanting. If we examine the phenomena taking place at the anode, we see that a current passes here through an electrolyte to the conducting core. Every passage of a current through an electrolyte must be accompanied by dissociation, the current being carried by the ions. We get therefore a movement of negative ions up into the electrode, and a deposition of electro-positive ions on the core (Fig. 90, *a*). In the same way at the kathode there will be a deposit of electro-negative ions on the core (Fig. 90, *d*), so we may say that the core is positively polarised at the anode and negatively polarised at the kathode.

FIG. 90

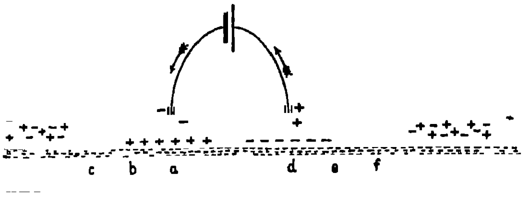


Diagram to show polarisation at the surface between conducting core and electrolyte sheath in a '*Kernleiter.*'

This polarisation, while opposing the primary current, will set up currents in the surrounding electrolytic sheath, as shown by the arrows in Fig. 91, the current passing from *a* to *b* and from *b* to *c* in the electrolyte, returning towards *a* in the core. Hence if we lead off from the sheath in the neighbourhood of the anode from *a* and *c*, a current will pass in the galvanometer from *a* to *c*, that is, along the core in the same direction as the intrapolar current. The same factors will cause an extrapolar current in the kathodic area, the katelectrotonic current.

FIG. 91.

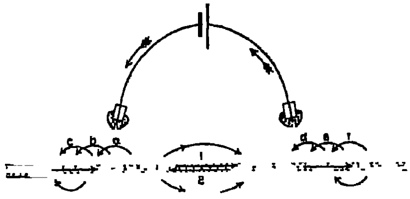


Diagram to show polarisation currents in a '*Kernleiter*,' or in a medullated nerve

It is evident that this polarisation will not disappear at once on breaking the polarising current. The nerve or nerve-model will still be positively polarised at the anode and negatively polarised at the kathode. On connecting therefore these two points with the galvanometer, we shall get a current in the opposite direction to the previous polarising current, viz. from anode to kathode (Fig. 92). This is the so-called *negative polarisation* of nerve. Similarly in the extrapolar regions of the nerve, we shall have currents in the *same* direction as the previous polarising current, as shown by the arrows. So far then the nerve behaves exactly like the mechanical model. If however we pass a very strong current through a nerve, and then quickly switch the nerve on to a galvanometer, we find a momentary current through the galvanometer in the same direction as the previous polarising current. This is known as *positive polarisation* of nerve. It is absolutely dependent on the living condition of the nerve, and is in fact an excitatory phenomenon due to the strong excitation which occurs at break of the current at the anode. Thus in the diagram (Fig. 93) a strong current is passing through the nerve from *a* to *k*. When this current is broken, excitation occurs, as we have already learnt, at the anode, and this excitatory state may, if the previous currents were strong, last two or three seconds. An excited tissue is however always negative towards adjacent unexcited tissue, and therefore if we connect *a* to *k*, there must be a current outside the nerve from *k* to *a*, and in the nerve from *a* to *k*,

FIG. 92.

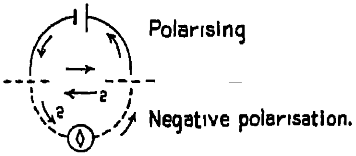


Diagram to show direction of the negative polarisation current.

FIG. 93.

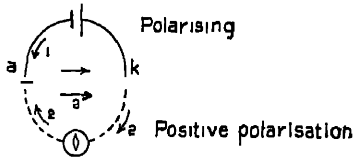


Diagram to show direction of the positive polarisation current, due to a break excitation at the anode.

viz. in the same direction as the polarising current. We see therefore that negative polarisation is due to polarisation occurring between an electrolytic sheath and a conducting core, whereas positive polarisation is hardly a polarisation effect at all but is a current of action.

Paradoxical contraction.—If the sciatic nerve of a frog be dissected out, and one of the two branches into which it divides be cut, and the *central* end of this branch stimulated, the muscles supplied by the other half of the nerve contract to each stimulus. Ligature or crushing of the nerve (x) between the points stimulated and the point which joins the main trunk puts a stop to this effect, showing that it is not due to a mere spread of current. The fibres passing down (n) are in fact stimulated by the electrotonic current developed in (x) during the passage of the exciting current.

Fig 94.

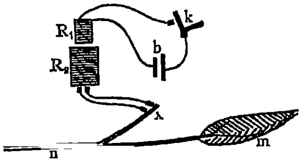


Diagram of arrangement for showing paradoxical contraction

SECTION 6

THE NATURE OF THE NERVOUS IMPULSE

It has been a subject of much debate what the exact nature of the nervous impulse really is, and how it is transmitted down the nerve. We have no other evidence of the passage of an impulse down a nerve than the current of action accompanying the impulse, and the result of the arrival of the impulse at the terminal organ, whether it be contraction of muscle, secretion of gland, or production of sensation in the central nervous apparatus. Since all these effects may be produced by electrical stimulation of the end-organs themselves, it has been thought that the wave of 'negativity' *is* the nervous impulse; that is to say, that the current produced in any given section of the nerve-fibre, when it is stimulated and so becomes negative, excites the adjacent segments or molecules, causing them to become negative, and thus setting up another current of action, which in its turn excites the molecules next in order; and that in this way the excitatory process travels the whole length of the nerve. A natural corollary of this view would be that the normal excitation of nerve-fibre in the brain or at the periphery is also brought about by electrical means. There are however considerable difficulties in the way of accepting this hypothesis. Although we can to a great extent imitate the results of the natural excitation of nerve-fibres by artificial electrical stimulation, yet the phenomena in the two cases do not run exactly parallel, and many differences are found to exist between the two forms of stimulation.

One of the most striking examples of this difference is the varying nature of the muscular contraction as produced by electrical stimulation or by natural (voluntary) stimulation. In dealing with the physiology of muscle, we saw reason to conclude that the natural contraction of muscle is a continuous one, although our only certain way of producing an approximate resemblance of such a contraction was by the use of *discontinuous* electrical stimulation.

An attempt has been recently made by Boruttau to explain the nerve-process, not as a wave of electrical change affecting the substance of the axis-cylinder itself, but as a propagated katelectrotonic current This observer found that by working with a 'platinum core model' ('*Kernleiter*') (Fig. 89) of considerable length, the katelectrotonic current was developed at one end of the model some appreciable time after a current had been sent in at the other end, thus resembling a current of action.

It is however impossible to explain all the electrical phenomena of nerve as due simply to polarisation. We might go so far as to assume that the excitatory effect at the kathode is due to negative polarisation, and that excitation at break, *i.e* at the anode, is caused by the sudden coming into existence of a negative polarisation current, but then it would be impossible to understand how the excitation, so produced at the anode, should give rise to a current so much exceeding the current which produced it, that it would appear in our external circuit as a current of positive polarisation We must in fact conclude that the axis-cylinder of the nerve is endowed with an energy of its own, which is let loose, so to speak, under the influence of chemical or electrical changes, just as the energy of a contracting muscle is set free by the exertion of an infinitesimal force applied as a stimulus. The nerve does not simply transmit the energy which is imparted to it, like a telegraph wire, but itself furnishes the energy of the descending nerve-process

Against this view might be urged the absence of phenomena of fatigue in nerve, as showing that nervous activity is not accompanied by any expenditure of energy or using up of material. But it must be remembered that this absence of fatigue holds good only for *medullated* nerve-fibres and is not found in non-medullated nerves, and even in medullated nerves the persistence of irritability is dependent on the continual supply of a certain small amount of oxygen It may therefore possibly be explained by a continual process of restitution taking place at the expense of the sheath. Fatigue is absent, not because nothing is used up, but because the assimilative changes exactly balance and make good the dissimilation involved in the propagation of a nervous impulse

CHAPTER VI

THE VASCULAR MECHANISM

SECTION 1

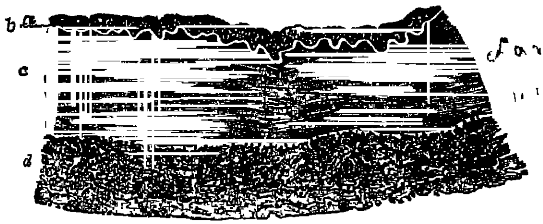
THE MECHANICAL PRINCIPLES OF THE CIRCULATION

Structure and Properties of the Blood-vessels

WE have now to study more fully the manner in which the continuous circulation of the blood through the body is carried on.

It will be remembered that the vascular system consists of a closed system of tubes divided into two circuits, known respectively as the greater or systemic circulation, and the lesser or pulmonary circulation, both connected with a central pumping organ, the heart, in the thorax. By means of the pumping action of the heart a continuous stream of blood is kept up from the right side, through the lungs, back to the left side of the heart, whence the blood is sent by the contraction of the left ventricle through all the rest of the body, and is returned by means of the superior and inferior venæ cavæ to the right side of the heart, so completing the double circuit. The blood-vessels vary considerably in structure according to their situation in the circuit. The vessels which carry the blood from the heart to the tissues, the arteries, are thick-walled, and contain an abundance of muscular and elastic elements in their walls. The typical medium-sized artery is described as consisting of three coats (Fig. 95): an *intima* lined by a continuous layer of flattened endothelial cells, which rest on a well-marked lamina of yellow elastic tissue; a *media* composed of unstriated muscular fibres arranged longitudinally and circularly; and an external coat or *adventitia* of fibrous tissue, with a number of longitudinal elastic fibres. Near the heart, in the great vessels such as the aorta and its larger branches, there is a preponderance of elastic tissue as compared with the muscular; and we find in the media alternate layers of muscle-fibres and fenestrated elastic membranes. In the smallest arteries, on the other hand, the arterioles, the elastic element entirely disappears, so that the wall consists of muscle-fibres, chiefly circular, lined by the endothelium. It is evident that in these latter vessels a contraction of their walls may result in an entire obliteration of their lumen. Judging simply from the structure of these vessels, one might guess that the chief function of the large arteries is to serve as elastic conduits, whereas that of the arterioles is to regulate the amount of blood flowing through them, and therefore the vascular supply to the tissues beyond. As the arteries branch there is a gradual enlargement of the total cross-section of the system of tubes, although the individual tubes become progressively smaller.

FIG 95.



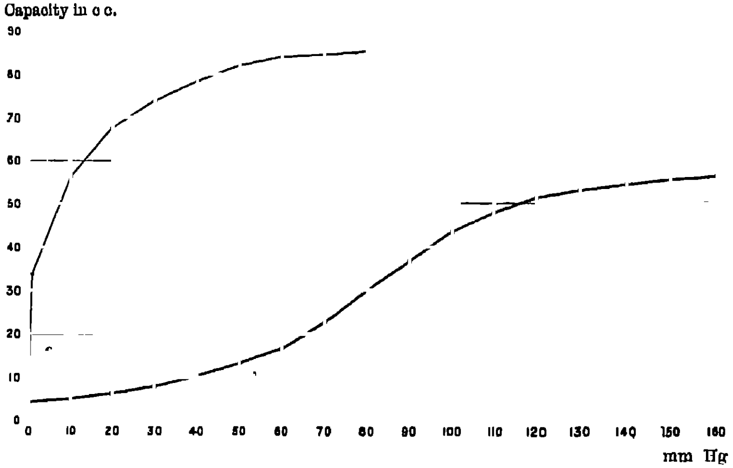
Transverse section of part of the wall of the posterior tibial artery (×75) *a*, endothelial and subendothelial layers of intima; *b*, lamina of elastic tissue; *c*, media consisting of muscle-fibres; *d*, adventitia (Schafer)

Although the muscle-fibres in the coats of the aorta and large arteries cannot by their contraction alter appreciably the flow of blood through these tubes, they have nevertheless an important function. Like all other kinds of unstriated muscle, they are extremely susceptible to changes of tension Any sudden increase in the pressure within the arteries will therefore excite these fibres to contract, so that the muscular tissue is able to support and reinforce the inert elastic tissue of the arterial wall in withstanding any sudden strain caused by a great rise of arterial pressure The muscle-fibres in the arteries have in fact the same protecting function on the connective tissue elements that is exercised (but by a more complex mechanism) by the skeletal muscles which send their tendons across a joint In the latter case, as we shall see later, any sudden stretching of the tendon excites the corresponding muscle to contract, so taking the strain of the joint movement off the ligamentous structures which surround it.

In the tissues themselves the blood flows through a close network of canals—the capillaries. In these all the elements of the vascular wall have disappeared, except the endothelium, so that the blood may come in closest possible connection with the tissues, without actual extravasation into the tissue-spaces. Owing to the great number of these capillaries, the vascular bed undergoes a sudden enormous enlargement as we proceed from arterioles to capillaries.

The blood is collected from the capillaries into small venous radicles, which unite to form larger and larger veins.

FIG 96



Curves of distensibility of an artery (thick line) and of a vein (thin line) The figures at the left side of the diagram represent the capacity of a section of the vessel when distended under a certain pressure, expressed by the figures on the base line in mm. Hg. (Constructed from figures given by Roy.)

Although in the vein we can distinguish by dissection the same three coats as in the typical artery, the thickness of the wall of the vein is very much less in proportion to its lumen than is the case with the arteries. There is moreover a diminution of the muscular and elastic, and a relative increase of the fibrous tissue-elements of the wall. A vein therefore collapses altogether, unless distended by some internal pressure.

This histological difference between veins and arteries is of considerable importance for the understanding of the distribution of pressures in the vascular system, since the distensibility and reaction to pressure of these vessels are conditioned by their structure. In Fig. 96 is represented the extensibility, *i.e.* the increase in capacity of an artery and a vein under gradually increasing internal pressure. It will be seen that an artery which has a certain capacity at zero pressure, gradually distends with increasing pressure. The increase in capacity is however small at first, and becomes most rapid between 90 and 110 mm. Hg. After this point every increment of pressure brings about a gradually diminishing increment of capacity. Thus a change of internal pressure causes the greatest change in capacity when the pressure in the artery corresponds, as we shall see, to the average arterial pressure in the normal animal.

In the vein, on the other hand, the capacity, which is nothing at zero pressure, becomes considerable on raising the pressure to 1 mm. Hg. A further rise of pressure to 10 mm. Hg. causes a considerable increase in volume, but from this point the increments of volume with rising pressure rapidly diminish. Whereas therefore the artery is most distensible at about 100 mm. Hg., the vein has its limits of optimum distensibility between 0 and 10 mm. Hg.

The Blood-pressure

If an artery in the living animal be cut across, blood spurts from it to a considerable height, escaping in jerks corresponding to every heart-beat. This fact, which shows the existence of a certain amount of pressure on the blood in the artery, may be illustrated in another way. If a vertical glass tube be connected with the central cut end of the carotid artery, the blood will rise in it to a height of three feet (in the rabbit), or still higher in the case of the dog, and remain about this height, rising a little with every heart-beat, and falling again between the heart-beats.

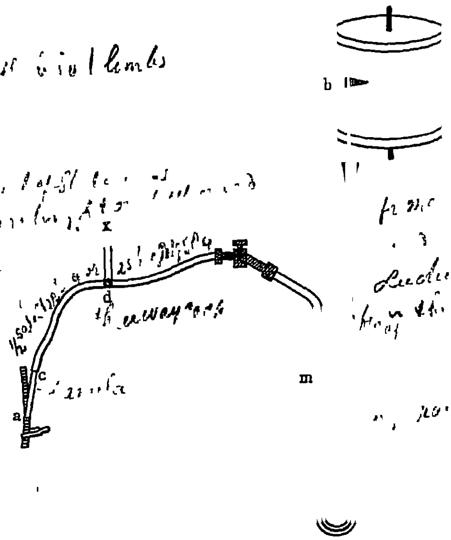
We thus see that the blood in the artery is under a constant pressure, which varies to a slight extent with the heart-beats, rising with and sinking between the beats, but never approaching the line of no pressure.

This blood-pressure may be more conveniently measured and its variations studied by means of an instrument called a manometer If we simply measure the pressure by inserting a vertical tube into the cut central end of an artery, the animal is injured by the loss of the blood which is necessary to fill the tube, and the experiment is soon stopped by the clotting of the blood in the tube

There are many different forms of manometer. The best for investigating changes in the mean arterial blood-pressure is Ludwig's mercurial manometer This instrument consists essentially of a U-tube with two vertical limbs about eighteen inches long This is half filled with clean mercury On the surface of the mercury in one limb is a float, from which a stiff fine rod (of steel or glass) rises, bearing on its upper end a writing point This point is adjusted so as to record its movements by scratching a white line on the smoked paper of a kymograph (A kymograph is merely an arrangement of revolving cylinders, moved by clockwork or other means, arranged to carry a roll of smoked paper) Instead of using the smoked paper, a pen may be fitted to the end of the vertical rod, and its excursions recorded in ink on a moving band of white paper

FIG 97

1. U tube with v [illegible] limbs
2 Clean Hg
3 A float
[illegible]



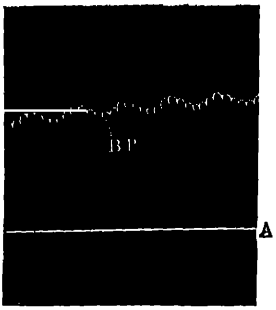
Arrangement of apparatus for taking blood-pressure tracing a, artery (carotid), c, cannula, d, three-way cock, m, mercurial manometer, b, drum covered with smoked paper

The other limb of the manometer is connected by a flexible rigid tube (such as lead) with a small tube or *cannula*, which is tied into the central end of the artery While the cannula is being tied, a clip is placed on the artery at (a), so as to prevent the blood escaping At (d) there is a three-way cock This is first turned so as to put the tube (x) into connection with the tube to the cannula, and the whole is then filled with a half-saturated solution of sodium sulphate, or a 25 per cent solution of magnesium sulphate The cock is then turned and the tube leading to the manometer filled in the same way

Both tubes being full, the solution is injected forcibly into (x), so as to raise the column of mercury about 150 mm The cock is then turned so that the manometer is put into connection with the artery. The clip is then taken off the artery. The column of mercury drops to about 120 mm (if the carotid of the dog is the artery used), and stops at about that level, rising and falling slightly with every heart-beat. The object of using sodium sulphate or magnesium sulphate solution is to delay clotting in the cannula.

On investigating in a similar manner the condition of the veins, we find quite a different state of things. If a vein be ligatured in any part of its course, it swells up on the distal side and shrinks on the side towards the heart. If it be cut across, the bleeding that occurs takes place nearly entirely from the distal end. The hæmorrhage moreover is of a different character from that which occurs when an artery is divided. The blood, instead of spurting out to a distance, wells up and is not increased or in any way affected by the heart-beat. If we connect a manometer with a vein, we find that the pressure amounts to a few mm. of mercury. Thus we see that the blood, which in the arteries is under high pressure and has an intermittent flow, by the time it has reached the veins is at a low pressure, and the flow has lost its intermittent character.

FIG. 98.



Blood-pressure tracing taken with mercurial manometer (from carotid of rabbit). A, abscissa or line of no pressure.

What is the cause of this change in the character of the flow? The blood in passing from arteries to veins has to traverse the arterioles and capillaries and in so doing meets with considerable resistance owing to the friction between the blood and the vessel-walls. Every time an artery divides, although each separate branch is smaller than the original branch from which it springs, the united sectional area of the two branches is greater, so that the sectional area of the capillaries exceeds by many hundred times that of the aorta. If this increase in the sectional area took place without division, its effect would be to lower resistance to the flow of blood. But if we consider for a moment the condition of the circulation of the capillaries, we see that the friction-lowering effect of increased area is much more than compensated for by the increased surface and therefore increased friction. Many of the capillaries are no wider than a single blood-corpuscle. The resistance of such a capillary system would be very large even to a stream of water, much more so then to a fluid which is somewhat viscid, and has suspended in it a number of solid particles.

Another factor however is involved in this question of resistance. The friction between the blood and the walls of the vessels depends not only on the extent of surface-contact, but also on the velocity of the blood. Owing to the great increase in area on passing from arterioles to capillaries, there is a sudden slowing-down of the blood-stream. The arterioles may be compared to small inlets into a wide lake. On this account it seems that the main resistance to the passage of blood through the tissues is situated, not in the capillaries but in the arterioles, and may be varied within very wide limits by alterations in the calibre of these vessels.

The main factors in converting the intermittent flow of the arteries into a constant flow through capillaries and veins and in maintaining a mean blood-pressure in the arteries are—

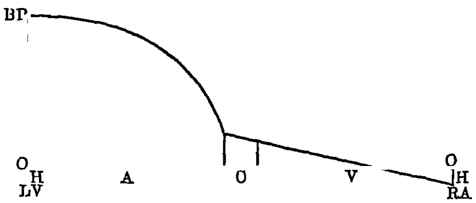
1. The contraction of the heart.
2. The peripheral resistance.
3. The elastic reaction of the arterial walls.

Since this is a purely mechanical question, it will be more easily understood by a simple illustration. The heart may be regarded as a pump, forcing a certain amount of blood (about 3 oz.) into the circulation at each stroke. If a pump be connected with a rigid tube, every time that a certain amount is forced into the beginning of the tube, an exactly equal quantity will be forced out at the other end at the same time. Increasing the peripheral resistance by partial closure of the end of the tube will not affect the intermittent character of the flow, but will merely serve to diminish the quantity thrown in, as well as the quantity which escapes at the other end of the tube, supposing that the work done by the pump is equal in both cases. If, instead of a rigid tube, we employ an elastic tube, and the end be left open so that no resistance is offered to the outflow of the fluid, the effect will be the same as when we used the rigid tube; the outflow will correspond exactly to the inflow, and will be just as intermittent. But now, if the end of the elastic tube be partially clamped, so as to increase the resistance to the outflow, there will be a marked difference between this effect and that produced by the rigid tube. Each stroke of the pump forces a certain amount of fluid into the tube. Owing to the peripheral resistance, this cannot all escape at once, and so part of the force of the pump is spent in distending the walls of the tube, and part of the fluid that was forced in remains in the tube. The distended elastic tube however tends to empty itself, and forces out the fluid which over-distends it before the next stroke of the pump occurs. So now the outflow may be divided into two parts,—one part which is forced out by the immediate effect of the stroke of the pump, and another part which is forced out by the elastic reaction of the tube between the strokes. If the strokes be rapidly repeated before the tube has time to thoroughly empty itself, it will get more and more distended. Greater distension means stronger elastic reaction, and therefore stronger outflow of fluid between the beats. This distension goes on increasing till the fluid forced out between the strokes by the elastic reaction of the wall of the tube is exactly equal to that entering at each stroke, and the outflow thus becomes continuous.

The same thing occurs in the living body. A man's heart at each beat or contraction forces about three ounces of blood into the already distended aorta. The first effect of this is to distend the aorta still further. The elastic reaction of the walls drives on another portion of blood, which distends the next segment of the arterial wall, and so the wave of distension is transmitted with gradually decreasing force along the arteries. This wave of distension is what we feel on the radial artery, or any exposed artery, as the pulse. After each heart-beat the arteries tend to return to their original size, and drive the blood on through the arterioles (the peripheral resistance) into the capillaries and so into the veins. By the time the blood has reached the veins, all trace of the heart-beat has disappeared, and the pressure has fallen to a few mm. of mercury.

The accompanying diagram represents roughly the distribution of pressure along the vascular system. The blood-pressure falls only slowly in the great arteries, as is shown by the line BP in the first part of section A. Towards the end of this section there is a sudden and extensive fall of pressure caused by the increase of resistance in the arterioles. In the capillaries (C) and in the veins (V) the blood-pressure once more falls gradually until, in the big veins near the heart, it may be negative.

FIG 99.



Scheme of blood-pressure in—A, the arteries; C, capillaries, and V, veins OO Line of no pressure. LV. Left ventricle RA. Right auricle. BP Height of blood-pressure

The following table may serve to give some idea of the probable average height of the blood-pressure at different parts of the vascular system in man. It must be remembered however that these pressures are all subject to considerable variations according to the physiological condition of the various parts and organs of the body.

Large arteries (e g. carotid)		+ 140 mm. mercury.	
Medium arteries (e g radial)		+ 110 mm	,,
Capillaries .	about	+ 15 to + 20 mm	mercury
Small veins of arm	.	+ 9 mm	,,
Portal vein .		+ 10 mm	,,
Inferior vena cava		+ 3 mm	,,
Large veins of neck	from 0 to	− 8 mm	,,

These main facts of the circulation can be well illustrated on a model made of indiarubber tubing, such as the artificial schema represented in Fig. 100. (B) is a basin of water, (e) an enema syringe, which can be used to force on water, and represents the heart. This is connected by an indiarubber tube (a) with a tube (c^2) which is packed with sponges to represent the peripheral resistance in the capillaries. From the distal end of (c^2) a tube (v) serves to conduct the fluid back to the basin. To side branches of (a) and (v) two mercurial manometers (m^1 and m^2) are connected, and these are arranged to write one below the other on the smoked surface of a kymograph. Another route for the fluid from (a) to (v) is afforded by the tube (c^1), which may be clamped at will. Tracings are first taken of the pressures on the arterial and venous sides with the tube (c^1) open, while the fluid is forced through the system by rhythmical compression

FIG. 100

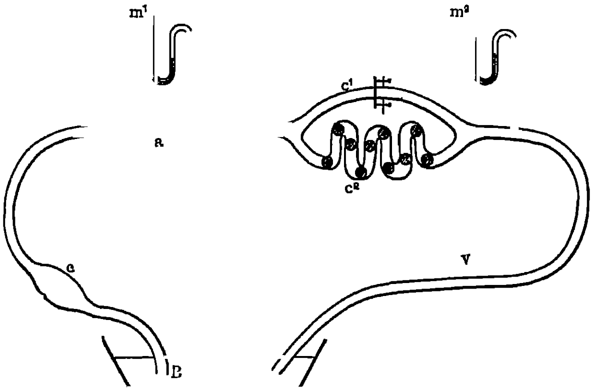
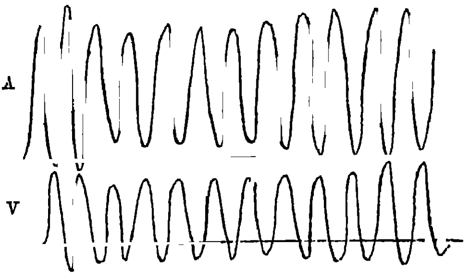


Diagram of artificial circulation schema

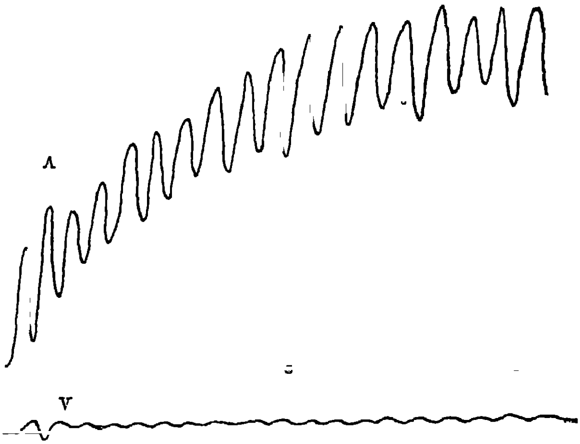
FIG 101



Tracing taken from artificial schema with slight peripheral resistance (Foster) A, arterial, V, venous manometer of the bulb of the enema. The fluid in passing from (a) to (v) has now practically no resistance to overcome, and accordingly we find the pressure-tracings of the two manometers (Fig. 101) are almost identical, the fluid escaping from the end of (v) at each stroke of the pump.

c^1 is now clamped so that all the fluid must pass through the tube (c^2) with a high resistance. Tracings are again taken (Fig. 102), and they show that the pressure on the arterial side at first rises with every beat till it has attained a certain height, where it remains stationary, merely oscillating with every stroke of the pump. The venous manometer, on the other hand, shows scarcely any rise of pressure, and its oscillations become less and less till they disappear, and the flow becomes continuous.

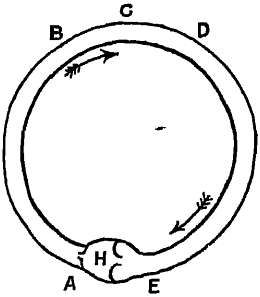
FIG. 102



Tracing from artificial schema with considerable peripheral resistance A, arterial, V, venous manometer

There is one feature in the circulation which is not represented in the above schema In the latter the system of tubes is open at both ends, and the amount of fluid supplied to the contracting heart-model is constant. In this model therefore, so long as the resistance in the circuit is constant, the pressure in all parts of the circuit will vary directly with the force of the heart-beat, and a rise of arterial pressure will be attended with a smaller rise of venous pressure, as shown in Fig 102 In the body however the blood-vessels form a closed circuit, containing a certain invariable quantity of fluid. We may imitate this condition in the schema by connecting the venous end of the tube with the supply-tube of the enema syringe, having previously over-filled the system to a slight extent Under these circumstances, so long as the heart is not beating, the pressure in all parts of the system will be the same, and this pressure, which may be called the mean general blood-pressure, amounts in a large dog to about 10 mm Hg. It will be seen at once that the pump or heart cannot alter this mean general pressure, but can only give rise to an unequal distribution of the pressure Thus it may diminish the pressure in the veins and increase the pressure in the arteries by pumping the fluid from the veins into the arteries We may take Fig 103 to represent the vascular system, which has a definite capacity and contains a definite quantity of blood If the heart (H) is not acting, and the fluid is motionless, the pressures at all parts of the system will be the same (10 mm. Hg) If now the heart begins to act, it pumps blood from the veins into the arteries, so that the latter become distended at the expense of the former, and the arterial pressure rises above, and the venous pressure sinks below, the mean pressure of the system It must be remembered that in the body the tubes forming the veins are much more distensible at low pressures than are the tubes on the arterial side Hence, when the heart begins to beat, we get a large rise of pressure on the arterial side (from 10 mm to 120 mm) and only a small fall of pressure on the venous side (from 10 mm to 5 mm, 0 mm, or near the heart about −5 mm) It is evident that in such a system, while the resistance remains constant, the venous pressure will vary inversely with the arterial pressure, and not directly with the latter, as is the case with an open circuit.

FIG. 103



There is one other important fact arising from the closed condition of the circulatory system In the body, changes in the peripheral resistance are effected by contractions of the smaller arteries and of some of the veins Now the contractions of these vessels not only increase the peripheral resistance, but also diminish the total capacity of the system, so that now we have the same amount of fluid as before enclosed in a smaller cavity This must mean an increased elastic distension of the walls of the cavity and a rise of the mean general pressure, so that a general contraction of the arterioles, the heart-beat being unchanged, may cause a rise of pressure both on arterial and venous sides.

It must therefore be remembered that, whenever a rise in arterial pressure is produced by active contraction of the smaller arteries, it is due to the coincidence of two factors—(*a*) increased peripheral resistance, (*b*) diminished capacity of vascular system.

In the living body there are two aids to the circulation on the venous side, which are not represented in our schema.

Firstly, nearly all the veins in the body possess valves, formed by reduplication of their lining membrane. These valves are so placed that they allow the passage of the blood only in one direction, viz. towards the heart. Thus any muscular contraction pressing on the veins can squeeze their blood only in one direction, and in this manner it assists the onward flow of blood.

Secondly, as we shall see in treating of respiration, the movement of the chest-walls at every inspiration causes a suction of the blood towards the thorax, and it is this aspiration of the thorax which gives rise to the negative pressure found in the big veins near the heart.

Velocity of the Blood-flow in the Vessels

Since the area of the blood-vessels increases progressively from aorta to capillaries, the rate of flow must decrease in like proportion. There are several methods by which the rate of flow in the larger arteries may be measured.

FIG 104

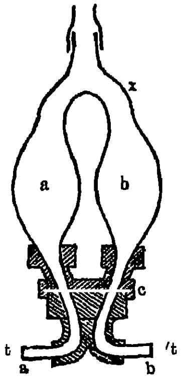


Diagram of Ludwig's '*Stromuhr*'

One of the most important historically is that devised by Ludwig, in which the '*Stromuhr*' is used. This (Fig. 104) consists of two oval glass vessels (a) and (b), connected above by means of a glass tube. The capacity of these vessels is accurately known. They are fixed at their lower ends in a metal disc (c), which is fitted on to another disc. The upper disc can be turned round on the lower disc. Through the latter run two tubes (t) and (t′), the upper ends of which are continuous with the vessels (a) and (b), and the lower ends, which are bent outwards in a horizontal direction, can be connected with the central and peripheral ends of a cut artery such as the carotid. In using this instrument the vessel (a), the connecting tube as far as the mark (x), and the two tubes (t) and (t′) are filled with defibrinated blood. The vessel (b) is filled up to the mark (x) with oil. The tube (t) is now fixed into the central and the other tube (t) into the peripheral end of a cut artery. As soon as the clips on the artery are released, blood flows from the artery through (t′) into (b), displacing the defibrinated blood in (a), which flows into the peripheral end of the artery. As soon as the inflowing blood has reached the mark (x), the whole upper part of the instrument is turned suddenly round 180°, so that (b) is now in communication with the tube (t). The blood, which is still flowing steadily into (t′), now rises into (a), driving the oil back into (b), and the blood in (b) onwards into the peripheral parts of the artery. As soon as the oil reaches its own level, the instrument is turned round again into its previous position, and so on. From the number of times that the '*Stromuhr*' has been turned round, we can reckon the amount of blood that has flowed through in a given time, and from this number, knowing the calibre of the artery, it is easy to compute the velocity of the blood in the artery.[1]

The earliest direct determinations of the velocity of the blood in the larger vessels were made by Volckmann by means of an instrument called the *hæmodromometer* This consists simply of a U-tube (Fig 105) of approximately the same size as the vessel in which the velocity is to be measured After being filled with normal salt solution it is connected by its two arms, *a* and *c*, with the proximal and distal ends of the cut vessel By means of the taps at *a* and *c*, the blood can either flow directly from *a* to *c*, or can be directed so as to flow entirely through the U-tube In this way the velocity of the blood is measured by seeing how long it takes for the blood to flow round the U-tube from *a* to *c*

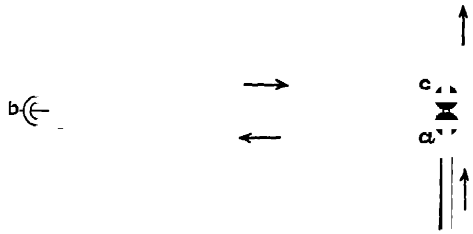
Both these methods give only the average velocity of the blood in the larger vessels In order to determine the rapid changes in velocity which occur during each pulse, several instruments have been devised.

The *hæmodromograph* of Marey consists of a wide tube with a window at one side covered in by a piece of elastic membrane. Through this membrane passes a writing-point which has an oar-shaped enlargement within the tube On placing the tube in the course of a blood-vessel so as to allow blood to flow through it, the blood-current causes a deflection of the flattened extremity of the lever which, communicated to the arm outside the tube, can be recorded on a blackened surface

---

[1] If we take v for velocity, m for volume of blood that has flowed through in a unit of time, and a for the sectional area of the artery, then $v = \frac{m}{a}$

FIG. 105



Hæmodromometer of Volckmann.

FIG 106

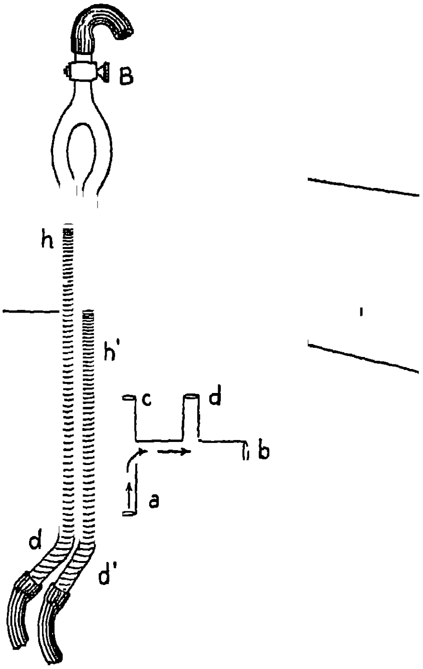
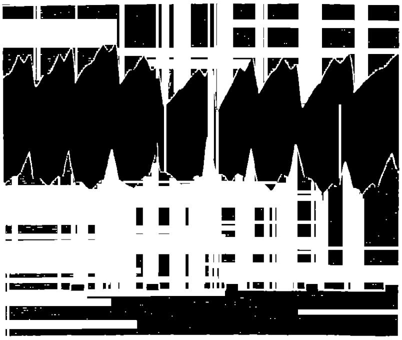


Diagram to show principle of construction of Cybulski's photo-hæmatachometer

A much better instrument for this purpose is the *photohæmatachometer* of Cybulski (Fig 106) If a current of blood be directed along the tube *ab* possessing two vertical side tubes *c* and *d*, the pressure at *c* will be greater than that at *d*, since at *c* the momentum of the moving mass of blood is added to the lateral pressure of the fluid. A tube of this shape is connected with an artery, such as the carotid, and the tubes *h* and *h'* are attached at the points *c* and *d* These two tubes are united at their upper extremities In this case, so long as the blood flows from *a* to *b*, the fluid in *h* will rise higher than in *h'*, and the difference in height of the fluid in the two tubes will be proportional to the velocity of the blood A graphic record of this difference of pressure is obtained by allowing a narrow beam of light to throw an image of the menisci of the two columns of fluid through a slit on to a moving photographic plate Such a record is given in Fig 107 The width of the black space at any point is proportional to the velocity of the blood at the moment at which this part of the record was being taken Of course this instrument has to be calibrated if we wish to determine the velocity of the blood in absolute measure In

Fig 107



Record of blood-velocity in the carotid artery of the rabbit (Cybulski)

Fig 107 the velocity at the point 1 and 1', corresponding to the cardiac systole, was 248 mm. per second At 2 and 2', corresponding to the dicrotic elevation, the velocity was also 248 mm At 3 and 3', towards the end of diastole, the velocity sank to 127 mm

The rate of flow in the capillaries may be measured by direct observation of the rate at which a blood-corpuscle moves along a capillary of the frog's web. It probably varies from ½ to 1 mm. per second. The area of the large veins near the heart (under normal pressure) is equal to about twice that of the arteries, and this relationship between veins and arteries holds good for the entire system. Hence, since the same amount of blood enters the heart as leaves it at each beat, the rate of flow in the veins must be about half that in the corresponding arteries.

It is also possible to measure the time taken up by the blood in traversing the whole of the circulation once, the 'total circulation time.' To this end a solution of sodium ferrocyanide is injected into the jugular vein on one side, and the time in seconds is noted that elapses before the salt can be detected in the samples of blood taken from the jugular vein of the other side. This time in the horse is thirty-one seconds, and in the dog seventeen seconds. In man it has been computed to be about twenty-three seconds.

Many other methods have been devised for the same end. Thus we may inject a strong solution of a colouring matter such as methylene blue into the jugular vein, and determine by actual inspection through the wall of the artery the moment at which the darkly coloured blood arrives at the point under observation. Or we may use the electrical method proposed by Stewart. a compensated current is sent through a small section of artery and a galvanometer A little strong salt solution is then injected into the jugular vein on the opposite side. As soon as the blood containing the stronger salt solution arrives at the artery, the resistance between the two electrodes is diminished, the compensation of the current is therefore at once destroyed, and the needle of the galvanometer is deflected

It must be noted that the 'total circulation time' does not represent the time it would take for the whole mass of blood to pass round the entire circulation once For in every tube the particles at the centre will move much more quickly than those in contact with the walls. In the living animal one blood corpuscle may pass rapidly from the aorta through the widely dilated arterioles of, *e g*, the thyroid gland, while another corpuscle may have to pass slowly through the constricted vessels of the skin of the foot before returning to the heart. The circulation time measured by the above methods is merely the shortest possible time in which a blood corpuscle, taking all the short cuts, can pass from right ventricle to left ventricle, and from left ventricle back to right ventricle. The *average* circulation time, *i e* the time necessary for the whole mass of the animal's blood to pass once through the heart, is probably two or three times as great as the times given above.

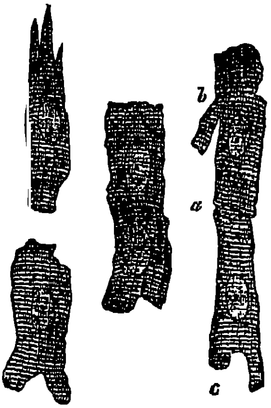
SECTION 2

THE CHANGES OCCURRING IN THE HEART AT EACH CONTRACTION

Anatomical Arrangements of the Heart-pump

We have already seen that the heart consists of four cavities, two auricles and two ventricles, and that each side of the heart, consisting of one auricle and ventricle, represents a pump which has for its function the driving of blood through the pulmonary or the systemic circulation. The muscular fibres forming the wall of the heart are so arranged that the contraction of the fibres causes a diminution, and the relaxation an enlargement of the heart-cavities The contractile tissue resembles voluntary muscle in presenting a cross and longitudinal striation, but differs from it in the fact that each contractile unit is not a fibre but a quadrilateral cell, having a single nucleus at its centre. These cells are arranged end to end so as to form fibres and possess no sarcolemma, the muscle-cells being apparently functionally continuous by means of fine intercellular protoplasmic bridges. In both its

FIG 108



Muscular fibres from the mammalian heart (× 425) (Schafer) histology and mode of contraction, cardiac muscle takes its place midway between unstriated and skeletal muscle.

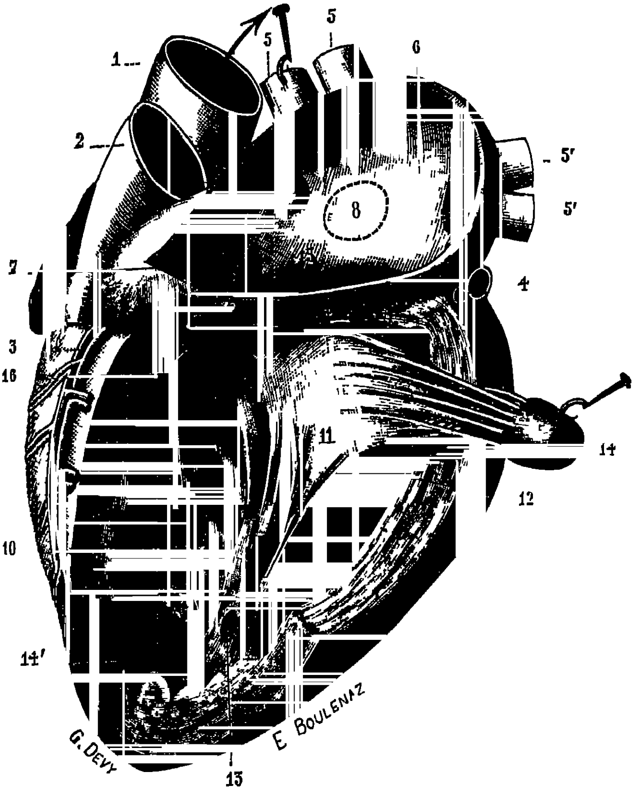
In the mammal the auricles are separated from the ventricles by a fibrous ring, from which most of the muscle-fibres of the two cavities take their origin. There is one band of fibres however, which are continuous across the auriculo-ventricular junction, taking a course down the intraventricular septum. It is this bundle which is responsible in the mammal for the propagation of the contraction from the auricles to the ventricles. In the ventricles the fibres have for the most part an oblique course, running from above downwards and to the left, sinking deeply into the substance of the ventricle towards its apex, where they make a spiral turn and are continued up again on the inner surface of the ventricle, ending in many cases in one of the papillary muscles. Besides these oblique fibres, there are a number of longitudinal and circular fibres, of which many are continuous over the two ventricles.

Corresponding with the greater amount of work thrown on the left ventricle, its wall is about twice as thick as that of the right ventricle, and on cutting a section through the two ventricles in a contracted condition, we see that the thin wall of the right ventricle lies in the form of a crescent round the circular left ventricle. The capacity of both ventricles is approximately equal, amounting in each case to about 140 c.c. (in complete relaxation).

Whereas the ventricles have to pump their contents into the arteries against a considerable pressure, the sole function of the auricles is to empty themselves into the relaxed and flaccid ventricles. We therefore find that the walls of the auricles are considerably thinner than those of the ventricles. Their muscle-fibres run both in a circular and a longitudinal direction, the circular fibres being continued round both auricles, special rings of circular fibres surrounding the openings of the great veins.

The endocardium which lines the heart-cavities is covered by a continuous layer of endothelium resting on a little fibrillated connective tissue and similar to that which lines the vascular system generally. The auriculo-ventricular orifices as well as the openings of the aorta and the pulmonary artery are guarded by valves permitting the passage of the blood only in one direction. The auriculo-ventricular valves are thin flaps of fibrous and elastic tissue covered on each side with endocardium and projecting downwards into the cavities of the ventricles. Their sail-like margins are connected by thin tendinous cords with nipple-shaped projections of the muscular walls of the ventricles, the so-called papillary muscles By these attachments the edges of the valves are kept close together and prevented from eversion under the strong pressure exerted by the contracting ventricles. These valves are two in number on the left side of the heart, forming the mitral valves, while on the right

FIG 109.



Left auricle and ventricle, with outer side cut away to show chief points in anatomy of heart (Testut) 1, aorta, 2, pulmonary artery, 3, ant coronary vessels, 5, 5', pulmonary veins, 6, left auricle, 7, auricular appendage, 10, cavity of left ventricle, 11, 12, mitral valves, 13, 14, papillary muscles, 16, arrow pointing to aortic orifice side of the heart, the auriculo-ventricular valves, though otherwise exactly similar to the mitral valves, are three in number and are called the tricuspid valves.

From a purely mechanical standpoint, the valves guarding the arterial orifices are much more perfect than those just described, which depend for their efficiency on the proper contraction of the ventricular wall and musculi papillares. Each orifice is guarded by three valves, which are semilunar in shape, are attached by their convex borders to the arterial wall, and present in the middle of their free border a small fibro-cartilaginous nodule, the *corpus Arantii*, from which fine elastic fibres pass to all parts of the valve. The extreme margin of each valve, the lunula, on each side of the corpus Arantii, is extremely thin, being formed of little more than the endocardium. Whenever the pressure in the arteries is greater than that in the ventricles, these valves are closed, and the thin margins come in contact with similar portions of adjacent valves, so preventing the reflux of a single drop of blood. The borders of the valves under these circumstances come together in the form of a star composed of three lines at angles of 120°, the three corpora Arantii being pressed together at the centre of the star.

No valves are found at the orifices of the great veins into the auricles, a reflux of blood in this situation during contraction of the heart being prevented by the contraction of the muscular rings round the veins, which always precedes the auricular contraction.

The heart, as well as the roots of the great vessels, lies almost free in a special serous cavity, the wall of which is formed by a tough fibrous membrane, the pericardium. This is attached below to the central tendon of the diaphragm and above to the arterial trunks. It is lined by a layer of endothelium continuous with a similar layer covering the surface of the heart. These two surfaces are kept continually moist by means of lymph, forming the pericardial fluid, so that the heart can move freely within the pericardium without friction. One of the chief functions of the pericardium appears to be to check an excessive dilatation of the heart during conditions attended by a rise of venous pressure.

The Phenomena of the Normal Beat

If we expose the heart of a mammal, as the rabbit, by opening the chest, the animal being kept alive by artificial respiration, it is possible to observe the sequence of events which happen at each contraction. The first thing to be noticed is a contraction of the great veins near the heart, which occurs simultaneously on the two sides. When the wave of contraction reaches the auricles, these contract shortly and sharply towards the ventricles, dragging down with them the auricular appendages, which also take part in the contraction and become pale and bloodless. This is followed almost immediately by the contraction of the ventricles, which is more prolonged and forcible. Contraction of both ventricles occurs synchronously. As we shall show later, contraction of the ventricles begins at the base and extends thence to the apex, but the propagation of this contraction-wave occurs so rapidly that it is impossible to follow it with the eye, all parts of the ventricle appearing to contract simultaneously. During contraction, the ventricle undergoes changes in shape, size, and position, becoming shorter from above downwards and changing in cross-section from an elliptical to a circular form, *i.e.* the heart becomes more conical. There is at the same time a twisting of the inferior parts of the ventricle, owing to the oblique course of the muscular fibres. If the pericardium is opened, this torsion causes a tilting of the apex forward and to the right with each contraction. In the normal condition, when the pericardium is intact, the apex remains almost stationary during contraction. This is owing to the fact that the pericardium is fixed externally, and the apex could not rise without causing a vacuum between it and the pericardium.
shortening of the long axis of the heart is rendered
le by a change in the position of the auriculo-ven-
r groove, which descends with every contraction, the
arteries elongating at the same time as they are
ed by the amount of blood thrown into them.

contraction or systole of the ventricles is followed by
nd relaxation, and they remain for some time at rest,
g simply passively filled with the blood flowing in through

the great veins and auricles. This period of relaxation and rest is called the diastole.

The Valvular Mechanisms of the Heart

We may now consider the effect of these cardiac events on the contained blood. During diastole the blood is flowing in a steady stream from the inferior and superior venæ cavæ into the right auricle and thence into the right ventricle, the propelling force being supplied by the systemic blood-pressure and the auxiliary forces already mentioned, *i.e.* muscular movement and aspiration of the thorax. As the great veins contract they simply hurry on their contained blood into the auricle, which immediately contracts on its contents, driving them through the open tricuspid valves into the right ventricle. It must be remembered that there are no valves at the mouths of the great veins (except in the great coronary sinus) to prevent reflux of blood into them during the auricular contraction. They are indeed unnecessary, the exclusive flow of blood into the ventricles being determined by the way in which the auricles contract owards the ventricles, and the low pressure in the ventricles uring diastole. The ventricles during the whole of diastole ave been getting more and more distended by the gradual nflow of blood. This distension is suddenly increased by he auricular contraction, and then follows almost immediately he contraction of the ventricles. As the blood is flowing rom auricles to ventricles, reflux currents or eddies must be ormed on the ventricular side of the tricuspid valves, ending to keep these from being widely opened. Directly e pressure rises in the ventricles, in consequence of the ontraction of their walls, the valves are forced back till eir edges come in contact and effectually prevent any eflux of blood into the auricles. The close apposition of e edges of the valves is further provided for by the tachment of the chordæ tendineæ of the papillary muscle to e adjacent valves. As the ventricle shortens, the papillary uscles contract, thus preventing the valves from being rced backwards and rendered incompetent. The effect of is contraction of the papillary muscles is that the auriculo-ntricular valves, which during the diastolic period form a truncated cone open towards the ventricle, are dragged still nearer to the ventricular wall, so that the blood is, as it were, expressed between two cones (heart-wall and valves). At the same time the contraction of the circular fibres at the base of the heart constricts the auriculo-ventricular orifices, so bringing the valves at their origin close together, and enabling their inner surfaces as well as their free edges to be apposed for a considerable extent (*v.* Fig. 110). The valves being thus closed, the pressure rises higher and higher in the ventricle, till it exceeds that in the pulmonary artery. Directly this is the case, the semilunar valves open and allow the ventricle to discharge its contents. The flow of blood from ventricle to artery goes on during the whole systole of the ventricle; during this time the semilunar valves are pressed outwards, but not close to the arterial wall, since they are probably kept in an intermediate position by the reflux currents or eddies set up in the blood on their arterial side. They thus form an orifice, triangular in shape with curved sides, presenting but little resistance to the onward flow of blood.

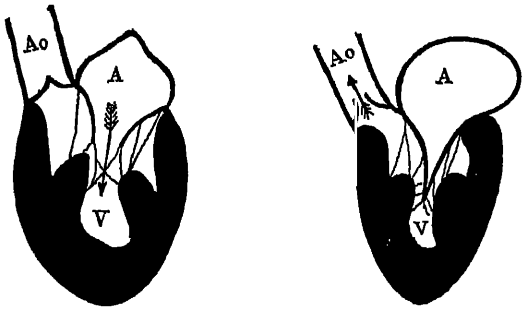


FIG 110 A

FIG. 110 B

Diagram to show position of mitral valves in diastole (110 A) and systole (110 B) A Auricle V. Ventricle Ao Aorta.

Directly the ventricular contraction ceases and the blood stops flowing, these reflux currents tend themselves to bring the valves together. At the same time the pressure in the right ventricle falls quickly to nothing, and the sudden difference in the pressures on the two sides of the valves causes them to shut tightly and sharply, giving rise to a click which is distinctly audible on listening with one's ear closely applied to the chest-wall, and represents the *second heart-sound.* The lunulæ of two adjacent valves are closely pressed together, thus preventing the possibility of the leakage of even a single drop of blood back into the ventricle

While these events are occurring on the right side of the heart, an exactly similar series is taking place on the left. During the diastole blood flows from the pulmonary veins to the left auricle and ventricle. The left auricle then contracts, and this is followed by the contraction of the left ventricle. The only difference between right and left sides consists in the fact that the pressure which has to be overcome in forcing blood into the aorta is much greater than that in the pulmonary artery, and so the left ventricle, having much more work to do, is much thicker, and contracts more forcibly, than the right. The closure and opening of the mitral and aortic valves occur in just the same way as the corresponding events affecting the tricuspid and pulmonary valves.

The Heart-sounds

If we apply our ear to the front of a person's chest (it is more convenient to use the stethoscope for the purpose), we hear two distinct sounds accompanying each beat of the heart, followed by a pause corresponding to the diastole. The sounds are compared to the syllables *lubb*, *dup*, the first sound being low-pitched and prolonged, the second sound high and sharp.

Thus the heart-sounds may be represented :

lubb, *dup* (pause), *lubb*, *dup* (pause)

The causation of the second sound is very simple, and may be considered first It is heard just over the second right costal cartilage, *i.e.* the place where the aorta lies nearest the surface.

It comes at the end of the systole, as determined by the hardening of the apex of the heart, felt as the apex-beat, and can be shown to be synchronous with the closure of the aortic valves. It is in fact caused by the sudden shutting and stretching of these valves that occur directly the heart ceases to contract and to force blood into the aorta. If the valves be hooked back (by means of a wire passed down a carotid artery) in an animal, the second sound disappears, and is replaced by a murmur caused by the blood rushing back into the ventricle at the end of the systole. The same disappearance of the normal second sound is often observed in cases where the valves are prevented from closing by diseased conditions.

The pulmonary and aortic valves generally close simultaneously. In some cases however the aortic may close slightly before the pulmonary, giving rise to a 'reduplicated second sound.' The pulmonary element of this sound is best heard over the second *left* cartilage.

FIG. 111.

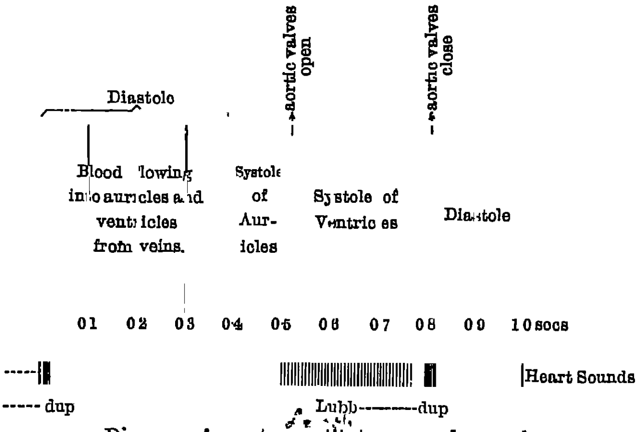


Diagram of events constituting a cardiac cycle.

The first sound has probably a twofold origin, viz. from the sudden closure of the auriculo-ventricular valves, and from the contraction of the thick muscular wall of the ventricle.

If the veins going to the heart be clamped, so that the heart can no longer be distended with blood nor the valves put on the stretch, the sound is altered in character but not abolished. The first sound may indeed be heard on listening with a stethoscope to the beat of an excised heart. It is said that two notes may be detected in the first sound—a high note of short duration due to closure of the valves, and a long low-pitched note due to the muscular contraction. This muscular element of the first sound has the same pitch as the sound produced by voluntary contracted muscle, and therefore as the resonance-tone of the ear.

This consideration prevents our arguing from the tone that a cardiac contraction is a tetanus. As we shall show later on, each ventricular contraction is analogous to a simple muscle-twitch, and not to a tetanus.

By means of these sounds we are able to determine to a certain extent the amount of time taken up by each phase of the cardiac cycle. In a healthy man the heart beats about seventy-two times per minute. So we may say that each systole with its corresponding diastole (cardiac cycle) is completed in about $\frac{8}{10}$ of a second.

This time is divided up in the following way:—Systole of auricle $\frac{1}{10}$ sec., systole of ventricle $\frac{3}{10}$ sec., diastole $\frac{4}{10}$ sec.

The relationship between the phases and heart-sounds is represented by Fig. 111.

The Pressure in the Heart Cavities during a Cardiac Cycle

We arrive at a clear idea of the events occurring during the ventricular systole by a study of the endocardiac pressure-curve.

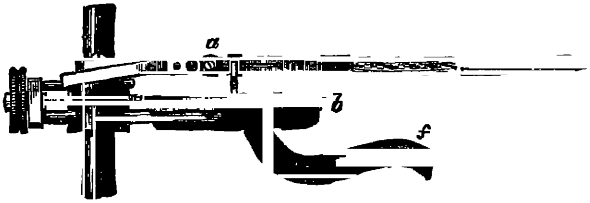
There are several methods by which the endocardiac pressure may be recorded. In one (Chauveau and Marey) a cardiac 'sound' is put down the jugular vein into the right auricle or ventricle, or down the carotid into the left ventricle. The cardiac sound is a stiff tube, having an elastic bag or 'ampulla' at the end that is to be inserted into the heart (Fig. 112). The upper end of the tube is connected with a tambour, which is a small round metal tray covered with delicate elastic membrane. To the top of the membrane a

FIG. 112.

Diagram of Marey's cardiac 'sound,' consisting of a long tube *a b*, terminating at one end in the ampulla *m*, which is covered with an elastic membrane The side-piece *c* serves to indicate the position of the ampulla after it has been introduced into the vessels writing lever is attached (Fig. 113) Any change of pressure on the ampulla causes a corresponding movement of the lever of the tambour, which may be recorded on a moving smoked surface.

Since this instrument is very easily set into vibrations, it is often difficult to know whether a given rise or depression on the tracing is to be taken as of cardiac or instrumental origin. Hence it is better to make the tambour very small, with thick rubber so as to limit the movements, and to fill it with saline fluid, which is also used to fill the tube connecting it to the heart. This is the principle of Hurthle's manometer (Fig. 114). It is evident that the mercurial manometer would be no good for this purpose, since the mercury column has far too much inertia to follow the rapid changes of pressure in the ventricles.

FIG 113



Marey's tambour *a*, axis of lever, *b*, metal tray covered with rubber membrane, and communicating by tube *f* with free end of cardiac sound

FIG. 114

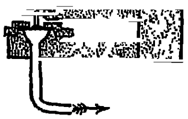


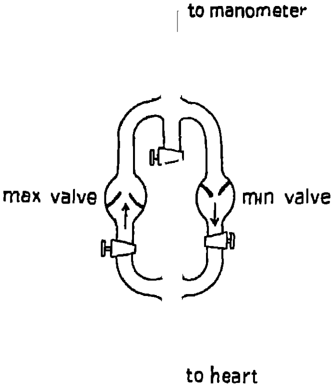
Diagram to show construction of Hurthle's membrane manometer

By the introduction of a valve in the tube leading from the manometer to the heart, it may be used as a maximum or minimum manometer. If the valve permits fluid to go only towards the heart, the manometer will indicate the minimum pressure ever attained during the cardiac cycle. If it be turned the other way, it will indicate the maximum pressure

(Fig. 115). In the dog the maximum pressure in the left ventricle may be 140 mm., in the right ventricle 60 mm., and in the right auricle about 20 mm. Hg. The use of the minimum manometer reveals the striking fact that, at some period of the cardiac cycle, there is a negative pressure in the ventricle; that is to say, the mercury is sucked up in the limbs of the manometer towards the heart. This negative pressure may amount to 30 or 40 mm. Hg. in the left ventricle, to 15 mm. in the right ventricle, and to 7 or 8 in the right auricle.

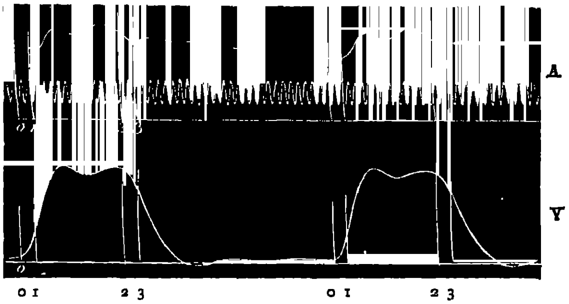
If however we register the variations of endocardiac pressure by means of a manometer which is sufficiently accurate to record the quick changes in pressure that occur in the ventricle with each heart-beat, we get a curve like Fig. 116. By registering this curve simultaneously with that of the blood-pressure in the aorta, we may determine what events are occurring during each phase of the curve. The auricular systole in some tracings causes a small rise of endocardiac pressure, represented by an elevation on the curve which would occur before the ordinate 0. It generally lasts about 0 05 second. It is not represented in the curve reproduced in Fig. 116. This is immediately followed by the ventricular

Fig. 115



v Frank's valve This is placed in the course of the tube between heart and manometer, so that the latter may be used as a maximum, minimum, or ordinary manometer according to the tap which is left open contraction, which lasts from 0 to 2. From 0 to 1 the ventricle is getting up pressure, so that at 1 the intraventricular pressure is equal to the aortic pressure. This process takes from 0·02 to 0·04 second. Directly the intraventricular pressure rises above this point the aortic valves open and blood is driven into the aorta. The outflow of blood lasts from 1 to 2, about 0·2 second. At 2 the ventricle suddenly relaxes, the period of relaxation occupying about 0·05 second. The flat part of the curve is often spoken of as the systolic plateau, and on an average occupies about 0·18 second. According to the condition of the heart and peripheral resistance, this plateau may present a gradual ascent or descent (*v.* Fig. 124).

FIG. 116.



Curve of intraventricular pressure, V, compared with pressure in aorta, A. Each vibration of time-marker = $\frac{1}{100}$ sec (Hurthle.)

Almost immediately after relaxation commences the intraventricular pressure falls below the aortic, so that the aortic valves close somewhere near the upper part of the descent (at 3).

Negative Pressure.—It will be noticed in the curve of endocardiac pressure that the line drawn by the lever descends slightly below the base line at the end of systole. This is the period at which the negative pressure occurs. This is however of such short duration that the most delicate manometers fail to show its maximum value. Several explanations have been suggested for the production of this negative pressure. When the flow of fluid through a tube is suddenly interrupted, the column of fluid, which has a certain degree of inertia, tends to go on, so that a negative pressure is produced in its rear. If however the negative pressure in the ventricle were due to the sudden cessation of flow through the first part of the aorta, we ought to obtain with the minimum manometer a negative pressure at the root of the aorta equal to that found in the ventricle. But this is not the case, so that the cause of the negative pressure must be sought in the ventricle itself. It is probably due to the fact that during ventricular contraction the base of the heart, including the orifices of the pulmonary artery and aorta, is constricted. Directly the ventricle relaxes, the pressure of blood in these two trunks causes a dilatation of their bases, and therefore of the base of the heart. This dilatation of the base of the heart increases its capacity, and so creates a negative pressure in the ventricular cavities. This mode of production of the negative pressure may be illustrated experimentally by connecting a manometer with the interior of either of the ventricles of an excised heart, that has ceased beating, and then forcing fluid into the aortic and pulmonary arteries. With each distension of the arteries so produced the mercury in the manometer sinks, showing the production of a negative pressure in the ventricles.

It is possible also that the ventricles exert some expanding force as they return from a contracted to an uncontracted condition.

The Cardiac Impulse (Apex-beat)

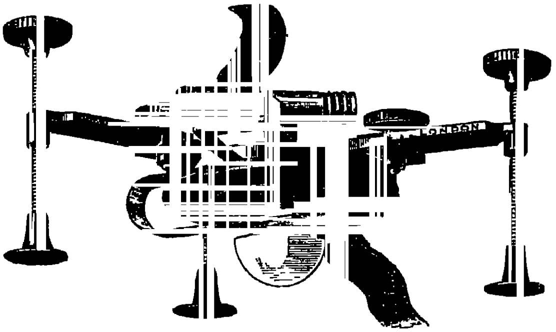
The movement of the heart at each contraction is communicated to the chest-wall, over a limited area of which it may be felt and seen, except in fat individuals. The region whence the pulsation of the chest-wall is most marked lies in the fifth intercostal space, a little to the median side of the left nipple. The pulsation is often spoken of as the apex-beat, and was formerly thought to be due to the twisting forward of the apex at each systole, but really lies considerably above the apex of the heart; and as we have already seen, the apex, so long as the pericardium is intact, is relatively motionless.

During diastole the ventricles form a flabby flattened cone lying against the chest wall and slightly deformed by the latter. In systole the ventricles contract forcibly on the contained fluid, and become hard and rigid, assuming the form of a rounded cone. This sudden recovery of shape and hardening of the ventricular walls pushes out the part of the chest-wall in immediate proximity to the ventricles, and so gives rise to the 'apex-beat.'

The cardiac impulse may be registered by means of a cardiograph. In nearly all forms of this instrument a button, resting on the chest-wall, transmits the movements of the latter to a tambour, which again is connected by a tube to a registering tambour. One such instrument is shown in Fig. 117.

The curves so obtained, which are known as *cardiograms*, may vary considerably in the same subject according to the pressure employed and the exact spot at which the tambour is applied. Their interpretation often presents considerable difficulties, owing to the fact that their form is conditioned by two factors, viz.:

Fig 117



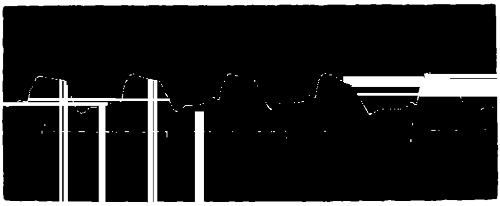
A cardiograph This is strapped round the chest, the central button is applied to the 'apex-beat' and its pressure on the chest-wall regulated by means of the three screws at the sides. The tube at the upper part of the instrument serves to connect the drum of the cardiograph with a registering tambour such as that shown in Fig 118

(1) The actual size (antero-posterior diameter) of the ventricles.

(2) The resistance to distortion (*i.e* the tension) of the ventricular wall. This factor will increase in importance with increasing pressure of the cardiograph button on the chest wall.

Fig. 118 represents a cardiographic tracing or cardiogram, which may be spoken of as typical. In order to interpret this curve, we must record at the same time either the intraventricular pressure in animals, or the heart-sounds in man.[1] Applying the latter method we may obtain the curve shown in Fig. 119. In this curve it will be seen that the first heart-sound, corresponding to the ventricular systole, begins, not at the commencement of the rise of the cardiogram, but at the notch near the top of the ascent. From this fact we may conclude that the first part of the ascent is caused by the auricular systole forcing blood into the ventricle, the ventri-

FIG 118



Cardiogram (Hürthle)

FIG 119.

Cardiogram (B) with simultaneous record of heart-sounds (A) (Hürthle) 1 Position of first heart-sound 2. Position of second heart-sound.

---

[1] This mechanical record of the heart-sounds has been successfully accomplished by Hürthle His method consists in an application of the microphone A special form of stethoscope is so arranged that by its means the vibrations corresponding to the heart sounds are transmitted to a contact between silver and carbon. Through this contact a strong current is passing This also passes through an electro magnet, which attracts an iron disc attached to the membrane of a Marey's tambour Any vibration transmitted to the carbon-silver contact alters its resistance, and so the strength of the current passing through the electro-magnet. In this way the heart-sounds can affect the pull exerted by the electro-magnet on the membrane of the tambour, and the change in the volume of the contained air is recorded by means of an ordinary registering tambour

cular systole being marked by the notch near the top of the curve. In Fig. 118, taken from the dog, the auricular curve is more distinct as a slight elevation preceding the rise due to the contraction of the ventricles. Other forms of curve however are often obtained, which show considerable differences from the endocardiac pressure, and are spoken of as atypical. They are often conditioned by a faulty position of the cardiograph.

utchinson &
Mowatt F. D.

Section 3

THE PULSE

Univ. Q. 1911 June 19th

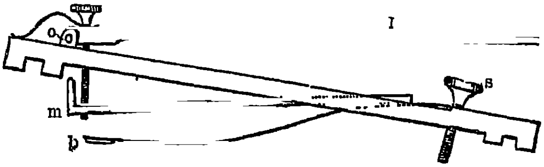
If the finger be placed on some artery, such as the radial, we feel an expansion of it occurring at regular intervals corresponding to the heart-beats. On the tracing of a mercurial manometer we saw a similar rise and fall produced by each heart-beat. So the pulse may be defined as the expansion of the artery under the increased blood-pressure caused by each ventricular systole. Just as the blood-pressure diminishes from heart to periphery, so the pulse diminishes in size as we get farther away from the heart. If the arterial system were perfectly rigid, the increased pressure due to the forcing of blood into it by each ventricular systole would occur almost simultaneously over every point of it. In the elastic distensible arteries however, the first effect of the inflow of blood into the aorta is to distend a section of the aorta nearest to the heart. The elastic reaction of this forces a portion of blood on into the next section, distending it in its turn. And so the increased pressure is transmitted from segment to segment of the arteries, in the form of a wave, at the velocity of about five metres per second. We must be careful not to confuse the velocity of the pulse-wave with that of the blood. The velocity of the blood in the aorta is not more than half a metre per second, and gets less and less towards the periphery. The pulse-wave may be compared to a wave produced by the wind travelling rapidly down a sluggishly flowing river.

We will make this difference clearer by an illustration. If the hindmost of a row of billiard balls be struck sharply with a cue, the foremost ball flies off and the others stop still. In this case the energy imparted to the first ball by the stroke has been transmitted from ball to ball, just as the effect of the ventricular contraction is transmitted from section to section of the arterial blood-stream. If the balls are struck so that the cue continues pressing on the hindmost after the stroke is delivered, the front ball flies off, while the others move slowly along in the direction of the stroke. In the arteries this continuous pressure is furnished by the elastic reaction of the arterial wall, and we see how the impact of the blood may travel quickly along as a wave of increased pressure, while the blood itself is moving slowly along, impelled by the elastic reaction of the arterial wall.

To study the pulse more fully it is necessary to obtain a graphic record of the expansion of the arteries, or, what comes to the same thing, of the exact changes in pressure which produce this expansion. The curve obtained with the mercurial manometer shows elevations corresponding to the pulse; but the instrument is far too sluggish to record the finer variations of pressure. For this purpose a manometer such as Hurthle's, which has very little inertia, must be used.

The expansion of the artery is registered by means of a lever which may be made to rest more or less heavily upon the artery, and the movements of which are recorded on a blackened surface. Such an instrument is called a *sphygmograph*. Of the many forms of sphygmographs, Marey's or Dudgeon's is perhaps the most convenient for clinical purposes (Fig. 120).

Fig 120

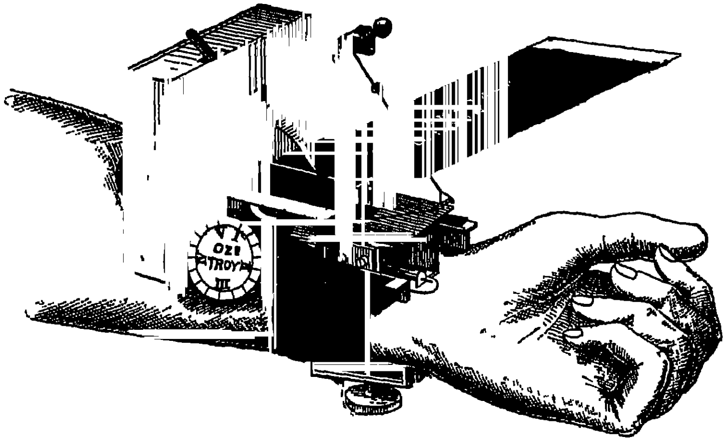


The principle of Marey's sphygmograph is shown in Fig 120 The button (b) is adjusted so as to press on the radial artery Its movements are transmitted to a lever (m) The screw on this works on a small cogged wheel at (o), which is also the axis of the writing lever (l) The movements of the button (b), thus transmitted to a point near the axis of (l), are reproduced by this lever highly magnified, and as such are recorded on a blackened surface The pressure on the artery can be adjusted by means of the screw (s)

Dudgeon's sphygmograph (Fig 121) is rather easier to use than Marey's, and is therefore largely employed for clinical purposes It is provided with a dial by which the pressure on the artery can be graduated, and has a small clockwork arrangement for moving along the slip of smoked paper on which the records are taken The arrangement of the levers in this form of sphygmograph is shown in Fig 122, where F is the (adjustable) spring bearing by its button P on the artery The up and down movements of P are transmitted to S being much magnified and converted into side to side movements The point of S rests on the blackened surface represented in section at A, and scratches on this, when moving, a magnified record of the expansion of the artery under the knob P

Either form of sphygmograph is generally applied to the radial artery since this is near the surface and is supported by bone, and the arm is well adapted for the application of the sphygmograph. The pulse-curve obtained by means of a sphygmograph varies according to the artery employed and the force with which the lever presses on the artery, but all the curves present the same general features

FIG. 121.



Dudgeon's sphygmograph, showing its mode of application to the radial artery.

FIG 122.

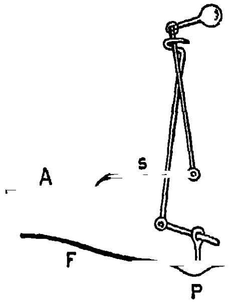
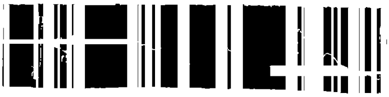


Diagram of arrangement of recording lever in Dudgeon's sphygmograph.

Fig. 123 represents a pulse-curve taken from the radial artery.

It will be noticed that the elevation due to the expansion of the artery is sudden and uninterrupted. We have already explained that this is due to the sudden pumping of blood into the first part of the aorta, whence the impulse is transmitted as a wave along the arteries. The curve descends gradually till the next beat occurs, since the elastic reaction of the arteries, which tends to keep up the pressure, acts more constantly and steadily than the heart-beat. On this descending part of the curve are seen two or three secondary elevations. (b) is the primary or 'percussion' wave, (c) the predicrotic or 'tidal' wave, and (e) the dicrotic wave. Elevations may occur on the curve after (e), which are called postdicrotic waves. It is better however, for reasons which we shall see presently, to class the elevations before the dicrotic notch (d) as systolic elevations, and those afterwards, including the dicrotic elevation itself, as diastolic. For the exact understanding of these elevations, it is necessary to take simultaneous tracings of the pressure in the left ventricle and the aorta. In this way we may dissociate the waves caused by the ventricular systole from those having their origin in the aorta. In Fig. 124 are represented typical tracings of cardiogram, intraventricular pressure, and aortic pressure taken simultaneously. The dotted lines are drawn through synchronous parts of the curves. Considering first the dotted part of Curve II and Curve IV,[1] we see that the contraction of the ventricle begins at A; the rise of intraventricular pressure from A to B is without effect on the aortic pulse; at B the intraventricular is exactly equal to the aortic pressure, and then rapidly rises above it. Since the aortic valves offer no resistance to the flow of blood from ventricles

FIG 123.



Pulse-curve from radial artery

---

[1] Curve IV in Fig 124 must be compared with the pulse-tracing taken from the radial artery in Fig 123 It will be seen that, apart from the fact that Fig 124, IV, is more lengthened out than Fig 123, owing to the great rapidity of the recording apparatus, the curves are practically similar

to aorta, they must open so soon as the intraventricular exceeds the aortic pressure, and this is shown to be the case by the rise of pressure in the aorta. From B to C the

FIG 124.

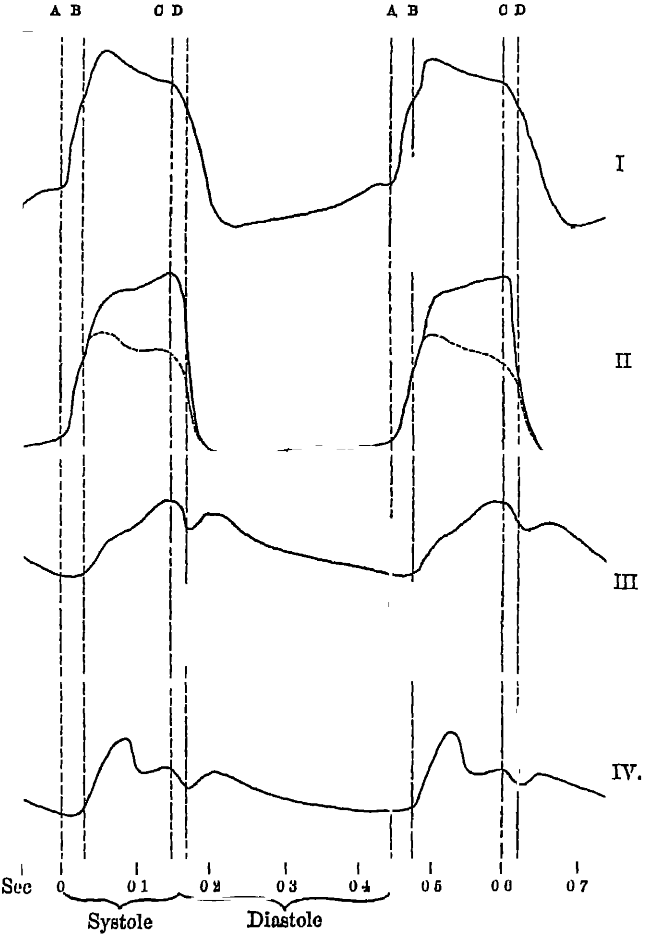


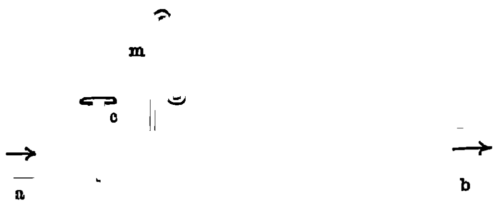
Diagram (after Hurthle) showing simultaneous cardiographic, endocardiac, and aortic curves I Cardiogram II Endocardiac pressure. III Aortic pressure. IV. Aortic pressure, corresponding to dotted endocardiac curve in II

ventricle is still contracting and forcing the blood into the already distended aorta, so causing a rise of pressure. At C the ventricle relaxes, the intraventricular pressure falls quickly, and at D has fallen below the aortic pressure. The aortic valves must now close, since the pressure is greater on their aortic side. The fall of pressure in the ventricle now goes on uninterruptedly, but in the aorta there is a sharp elevation immediately after D. This elevation is the dicrotic wave. We thus see that it comes immediately after closure of the aortic valves.

There are several factors at work tending to produce a secondary wave at this point.

If a column of fluid moving along a tube (a, b, Fig. 125) provided with a stopcock (c) and a manometer (m) be suddenly checked by turning the cock (c), the column in front of the cock, having a certain momentum, will tend to go on moving, and therefore produce a suction or negative pressure behind it. This will be indicated by a depression of the level of the manometer. The fluid will flow back to fill this partial vacuum, and so a series of oscillations in the column, getting smaller and smaller, are produced, which are recorded by the manometer as oscillations of pressure. The same thing must occur in the beginning of the aorta, when the inflow of blood from the ventricle suddenly ceases with the end of the ventricular contraction. In this case however the oscillations are increased by the elastic reaction of the arterial wall, just as a weight which is suddenly applied to a piece of elastic swings up and down before it comes to rest with the elastic in a permanent condition of tension. These two factors combine in producing a negative wave in the beginning of the aorta at the end of the ventricular systole, the blood driven up against the aortic valves closing them tightly

Fig 125



and putting them on the stretch. The negative wave, even in the rigid tube, is followed by a positive wave in the opposite direction. In the aorta this positive wave is increased by the elastic reaction of the stretched aortic valves, so that we may regard the blood as being driven up against them by the negative pressure, and then rebounding like a billiard ball from the elastic cushion, to give rise to the dicrotic elevation.

The post-dicrotic waves, when present, are probably due to the waves of oscillation.

We have now to consider the elevations in the first part of the curve, which we have spoken of as systolic elevations, and which include the pre-dicrotic elevation. It will be seen that they are also represented on the ventricular curve, and occur while the aortic valves are open and blood is flowing from the ventricle into the aorta. They are probably due to the elastic vibrations of the aortic wall, and perhaps of the heart-wall itself, started by a sudden increase of tension in the aorta and heart.

The general form of the pulse-curve varies with changes in the heart, in the arteries, and in the peripheral resistance. Thus some curves may present secondary elevations on the ascending part, as in Fig. 124, III, and are called *anacrotic*, while in others all secondary elevations occur on the descending part. This latter type is called *katacrotic*, and is the tracing usually obtained from a normal radial artery. By comparing these two types of curves with the corresponding intraventricular pressures, we find that, in both cases, blood is flowing into the aorta during the whole time from the beginning of the primary elevation to the notch just before the dicrotic elevation. This is shown by the fact that the intraventricular pressure is all this time slightly higher than the aortic pressure. So long as this is the case blood must flow from ventricle into aorta. (This fact shows that there is normally no part of the cardiac cycle during which the ventricle remains contracted and empty, the ventricle in all cases relaxing before it has completely emptied itself of blood.)

Now it is easy to see the conditions which determine whether the systolic plateau shall be ascending or descending, and therefore when the pulse shall be anacrotic or katacrotic. If, after the first sudden rise of pressure in the aorta, the blood can escape more rapidly through the peripheral resistance than it is thrown into the beginning of the aorta, the systolic plateau will sink, and a katacrotic pulse tracing is obtained. If on the other hand the peripheral resistance is high, or an extra large amount of blood is thrown into the aorta at each stroke of the heart (*e.g.* by prolongation of the diastole), the aortic pressure will rise so long as blood is flowing in, and we get an ascending systolic plateau and an anacrotic pulse. Thus we obtain an anacrotic pulse in old people with Bright's disease, in whom the peripheral resistance is very high, and also in animals when the heart is slowed by vagus action.

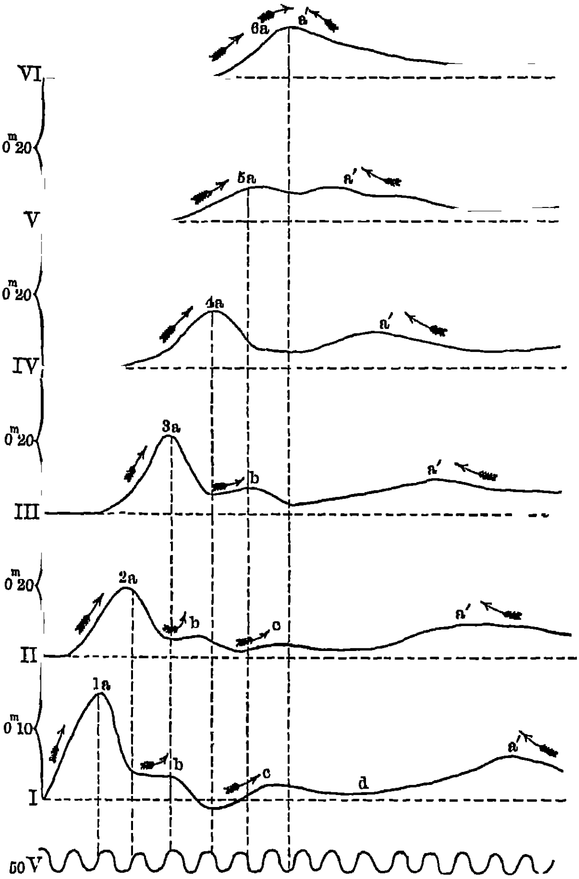
The production of the dicrotic elevation is favoured by any influence which increases the elastic resiliency of the arteries or causes the primary elevation of the pulse to be rapid and sharp. Thus it is much more pronounced in young people than in old people, whose arteries have become rigid. Where the peripheral resistance is low through relaxation of the arterioles, and the heart is beating forcibly, as in many cases of fever and also to some extent after a good meal with alcohol, the dicrotic elevation becomes very marked. Under such circumstances it may be easily felt with the finger at the wrist, and in many cases the mistake has been committed of taking the dicrotic wave for a normal beat, and so doubling the rate of the pulse.

In tracings of the artificial pulse obtained from the arterial schema, secondary elevations are observed on the descending part of the curve, which are not explained in any of the above-mentioned ways These waves are the reflections of the primary wave from the peripheral resistance This is shown by the fact that the nearer to the peripheral resistance we record the pulsation, the nearer is the secondary to the primary wave Near the pump the two waves may be separated by a considerable interval (Fig. 126).

It has been thought that some of the elevations in the normal pulse-curve could be explained as reflected waves This theory is at once excluded by the fact that wherever we take the pulse tracing, whether from the aorta, carotid, radial, or dorsalis pedis, the secondary elevations are always situated the same distance from the beginning of the primary elevation, showing that all these waves are centrifugal, and have their origin in the beginning of the arterial system

Besides, a single reflected wave from the multitudinous peripheral divisions would be impossible, as the reflected waves from any one part would be interfered with and destroyed by the reflected waves coming from all the other parts A reflected wave would be increased by a high peripheral resistance, and not diminished as the dicrotic wave is.

FIG. 126.



Pulse-curves described by a series of sphygmographic levers placed at intervals of 20 cm. from each other along an elastic tube, into which fluid is forced by the sudden stroke of a pump. The pulse-wave is travelling from left to right, as indicated by the arrows over the primary (a) and secondary (b, c) pulse-waves. The dotted vertical lines drawn from the summit of the several primary waves to the tuning-fork curve below, each complete vibration of which occupies $\frac{1}{50}$ sec., allow the time to be measured which is taken up by the wave in passing along 20 cm. of the tubing. The waves (a') are waves *reflected* from the closed distal end of the tubing; this is indicated by the direction of the arrows. It will be observed that in the more distant lever (VI) the reflected wave, having but a slight distance to travel, becomes fused with the primary wave. (From Foster, after Marey.)

Venous Pulse.—Under certain conditions the pulse may be carried on from the arteries through the capillaries into the veins, giving rise to a venous pulse. Thus stimulation of the chorda tympani nerve causes all the arterioles of the submaxillary gland to dilate. The peripheral resistance is in this manner so lowered that it is insufficient to destroy the arterial pulse, and on cutting the veins from the gland blood spurts intermittently from their peripheral end. Lowering the resistance in this case has produced the same effect as unclamping the tube c^1 (Fig. 100) in the arterial schema.

On attaching a manometer to the central end of the superior or inferior vena cava, elevations are observed corresponding to the variations in the auricular pressure. These are double for each heart-beat. While the ventricle is contracting there is a slow rise, due to the fact that the blood, which is flowing in from the veins, cannot escape into the ventricle, and so distends the auricle; a second short sharp elevation of pressure is produced by the auricular systole.

Alterations of venous pressure, determined by the respiratory movements, are also to be observed in the great veins, the pressure sinking during inspiration and rising during expiration. These may be spoken of as the respiratory venous pulse.

SECTION 4

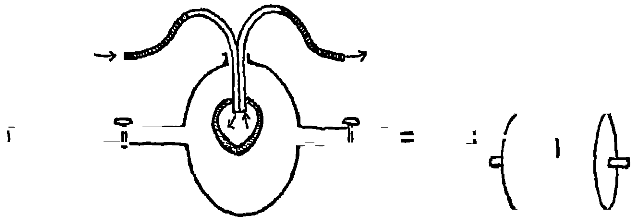
CARDIAC RHYTHM

If the heart be rapidly cut out of the body, it will continue beating in a normal fashion for some time—in the case of mammals from five to ten minutes; in the case of cold-blooded animals, such as the frog or tortoise, for some hours or even days. We say therefore that the rhythm of the heart is automatic; and we have now to discuss wherein this automatic rhythmicity lies. The circumstance that the cold-blooded heart goes on beating so long, when severed from all connection with the body, has caused it to be much used in investigations on the subject, and from it most of our knowledge has been acquired.

Methods of Investigation

The contractions of the frog's heart may be recorded by magnifying its movements by means of a light lever, one end of which rests upon the ventricle, while the other end is made to write upon a blackened surface—or, as in Gaskell's method, by clamping the heart in the auriculo-ventricular groove, and attaching threads from auricle and ventricle to two levers which are arranged to write one over the other. Or we may register the changes in the intraventricular pressure by allowing dilute blood or some other nutrient fluid to flow through a perfusion cannula tied into the ventricle, and attaching the exit-tube of the cannula to a small mercurial manometer.

FIG 127.



Schafer's heart plethysmograph.

Another way is to register the changes in volume of the heart (Fig. 127). The ventricle is tied round a perfusion cannula, and is inserted into an air-tight vessel containing oil. On one side of the vessel is a tube, in which a lightly moving piston is fitted, to which a writing lever is attached. Fluid is passed through the heart by the perfusion cannula at a constant pressure. The changes in volume are indicated by the movements of the piston.

Anatomy of the Frog's Heart

The frog's heart differs anatomically in several respects from the mammalian heart. It consists of sinus venosus, two auricles, one ventricle, and bulbus arteriosus. The venous blood from the body flows into the sinus venosus by the three venæ cavæ, and thence into the right auricle. The left auricle receives the blood from the lungs. The ventricle thus receives mixed arterial and venous blood.

FIG. 128

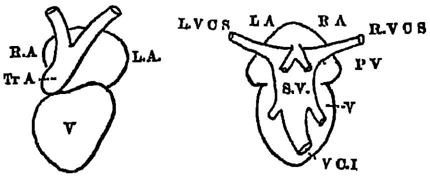


Diagram of frog's heart (after Cyon) V Ventricle R A., L.A. Right and left auricles (atrium) S V Sinus venosus P.V Pulmonary veins L V.C.S and R V C S Left and right superior vena cava. V C I Vena cava inferior Tr A Truncus arteriosus

The muscular fibres of the heart are less highly developed than those of the mammalian heart. They are spindle-shaped, and only dimly cross-striated. The cross-striation becomes more distinctly marked as we proceed from sinus to ventricle, the sinus muscle-fibre representing the most primitive condition. There is complete muscular continuity between all the cavities of the heart. The circular ring of muscle at the junctions of sinus with auricles, and of auricles with ventricles, presents only slight traces of cross-striation.

The heart is well supplied with nerve-fibres and ganglion-cells. The two vagi enter the sinus venosus, and branch just under the pericardium. Here they become connected with a collection of nerve-cells, spoken of as Remak's ganglion.

From the sinus, the two vagi, now called septal nerves, pass down in the interauricular septum, one in front and the other behind. Near the auriculo-ventricular groove they enter two collections of ganglion cells, called Bidder's ganglia. From these ganglia non-medullated fibres are distributed to surrounding parts of the auricle and to the whole of the ventricle. In the upper third of the ventricle occur scattered ganglion-cells attached to the nerve-fibres. These are quite absent in the lower half or two thirds

The Automatic Contraction of the Frog's Heart

The frog's heart in the body, or when removed from the body intact, beats regularly, the contraction starting in the sinus, then travelling to auricles, ventricle, and bulbus. If however the heart be removed by cutting it across the sino-auricular junction, or if the auricles be functionally separated from the sinus by a ligature round this junction (Stannius' ligature), the auricles and ventricle stop dead in an uncontracted condition (diastole) while the sinus goes on beating regularly. After the lapse of a period varying from five minutes to half an hour the detached part of the heart begins to beat, at first slowly and then more rapidly, but never attaining the rate of the sinus. The auricles beat first, and then the ventricle.

If now the ventricle be cut away by an incision in the auriculo-ventricular groove from the auricles, the latter go on beating; while the former, after a few beats due to the excitation of the incision, stops still, and only after a considerable time may begin again to contract very slowly.

On the other hand, a ventricle-apex preparation (that is to say, the lower two thirds of the ventricle separated functionally from the rest of the heart) never beats again under normal circumstances. To single stimuli it responds with a single beat, not with a series of beats as the whole heart does.

If the lower third of the ventricle be separated functionally in the living frog by crushing the ring of tissue between it and the upper third, it never gives a spontaneous beat again, although it is under the most normal conditions possible in the circumstances. There is thus a descending scale of automatic power in the different parts of the frog's heart—from the sinus, where it is highest, to the lower part of the ventricle, where it is apparently absent. From this fact it has been thought that the automaticity of the frog's heart is dependent on the ganglia present in it. The contraction was supposed to be started by impulses proceeding from the sinus ganglion. If this were cut off, Bidder's ganglia, or the scattered cells in the upper third of the ventricle, could, it was thought, take up its task of originating impulses. The muscle-cells under this hypothesis act as the servants of the ganglion cells, just as the voluntary muscles wait on the commands of the cells in the spinal cord and brain.

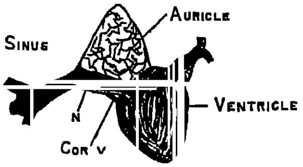
But we have evidence that the muscle-cells do not play so subordinate a part as this in the heart, and that the larger ganglia, at any rate, are of very little importance in initiating the rhythm. Remak's and Bidder's ganglia may, with care, be excised without markedly interfering with the normal rhythm or sequence of contraction. The ventricle apex may be made to contract rhythmically if the pressure on its interior be slightly increased, either by clamping the aorta in the living frog, or by supplying a ventricle-apex preparation through a perfusion cannula with diluted blood at a pressure rather above the frog's normal blood-pressure. A strip cut from the apex of the tortoise's ventricle may be made to beat rhythmically, if it be hung in a moist chamber and stimulated at intervals with weak induction-shocks. After a time the strip begins to beat of its own accord, and beats rhythmically for many hours.

It seems probable then that the automaticity of the heart is inherent in its *muscular* tissue, the difference in the automatic power of the various parts being dependent on their different histological characters. The lowly differentiated sinus-cell has high rhythmic power and a quick rhythm of beat, but contracts feebly. The more highly differentiated ventricle-cell has only slight rhythmic power, but beats forcibly, and is a good servant of the sinus. If all parts of the heart had equal rhythmic power or the same rate of rhythm, there would be no reason why any one part of the heart more than another should initiate the beat. As it is, the beat always starts in the part beating with the greater frequency, viz. the sinus. In some animals this difference of rhythmic power is less marked, and the contraction may start from either end of the heart. Even in the frog, the heart-cavities may be made to contract with a reversed sequence, *i.e.* in the order of ventricle, auricles, sinus, by artificially stimulating the ventricle at a rate exceeding the normal sinus rhythm.

Propagation of the Wave of Contraction in the Frog's Heart

The next question is: How is the excitatory process conducted from sinus to auricles and thence to ventricle? It was formerly thought that this conduction was effected through nerves. It has however been shown by Gaskell in the tortoise's heart, where the nerve-trunks run apart from the auricles from sinus to ventricle, that division of these trunks causes no alteration in the rhythm of the ventricle. If however the auricles be cut through, leaving the ventricle attached to the sinus by the nerve-trunks, the sequence of beats is utterly lost.

FIG. 129.



Tortoise's heart (after Gaskell) as it appears when suspended for registering the auricular and ventricular contractions N, nerve-trunk with fibres connecting Remak's and Bidder's ganglia; Cor v, coronary vein.

The auricles may be slit up by interdigitating cuts, by which all nerve-trunks must infallibly be divided, and yet the wave of contraction passes from the sinus over the auricles round the interdigitating cuts to the ventricle.

There is a distinct pause between the contractions of auricles and ventricle. This was supposed to point to the intermediation of nerves in the transmission of the excitatory process across the groove. The pause however is probably due to the fact that the muscle-cells forming the auriculo-ventricular ring are very slightly differentiated, and so contract and conduct slowly, *i.e.* this muscular ring presents a partial 'block.'

The auricles may be made to beat in two halves by merely dividing the sinus half from the ventricular half, leaving them connected by a very narrow strip of auricular wall. In this way a block is produced at the cut. The sinus contracts, then the upper part of the auricles. This is followed by a distinct pause, during which the excitatory process is passing the block. The ventricular half of the auricles then contracts, followed by the ventricle and bulbus.

We may conclude that a normal contraction of the frog's heart originates in the muscular wall of the sinus, and travels as a wave from muscle-cell to muscle-cell, over the auricles and ventricle; the apparent pauses between sinus and auricles and auricles and ventricle being due to the low conducting power of the muscular tissue connecting these cavities.

It will be seen from what we have already said that the contraction of the heart is to be looked upon as a single contraction wave, propagated from one end of the heart to the other, just as a wave of contraction passes along the sartorius (though at much quicker rate and of shorter duration) when this muscle is stimulated at one end.

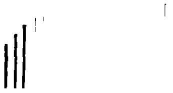
Some Properties of the Cardiac Muscle

Contraction always maximal.—In several points however the properties of cardiac muscle differ from those of ordinary striated muscle. Its automaticity and power of responding rhythmically to continuous stimuli have already been mentioned. The height of contraction of a voluntary muscle is, within certain limits, proportional to the strength of stimulus. If the ventricle, rendered motionless by a Stannius' ligature, be stimulated with a single induction-shock, it always responds with a maximal contraction, whether the stimulus applied be minimal or maximal. There is thus no proportionality in the heart between strength of stimulus and height of contraction. The heart, if it contracts at all, always contracts to its utmost. The height of the contraction is dependent on the condition of the muscle at the time, but not on the strength of stimulus.

'Staircase' phenomenon.—If the frog's ventricle has been at rest for some time, a single contraction makes the heart

more excitable and in a better condition. So if, in a Stannius' preparation, we excite the ventricle with single induction-shocks once in every 10 seconds, the first four or five contractions form an ascending series, each contraction being rather higher than the preceding one.

FIG. 180.



Group of pulsations showing 'staircase' character.

Summation of stimuli.—In a similar preparation it is easy to demonstrate the summation of stimuli, which was described in dealing with unstriped muscle. If the ventricle of a Stannius' preparation be stimulated with inadequate shocks, it is found, on repeating these shocks at short intervals of time, that they become adequate, and cause a contraction of the ventricle. The subsequent contractions then show the progressive augmentation just described as the 'staircase.'

Influence of tension.—Much the most important factor affecting the strength of the cardiac contractions is the tension of the muscle-fibres. Within certain limits the energy of contraction of the cardiac muscle increases with the tension (*i.e.* resistance to shortening) to which the muscle-fibre is exposed. This effect can be seen when the resistance to the outflow of blood from the heart is increased, and the resistance is only experienced *during* the contraction of the heart-muscle. It is much better marked however if the alterations of tension take place before the contraction, *i.e.* during the diastole. In this case we observe that within wide limits the heart contracts more forcibly the greater its distension during the diastolic period. This effect of the initial tension on the force of the ventricular beats is well shown in Fig. 181, representing tracings taken from the frog's ventricle under increasing initial tensions. In this case the heart was contracting isometrically, *i.e.* against a strong elastic resistance, so that the curves are a true representation of the actual energy displayed by the heart. In all cases the heart was unable to expel any of its contents, so that the difference in height of the curves is due solely to period, in which stimuli applied to the heart have no effect. This will be followed by a period in which a stimulus is followed by an extra contraction, but with a prolonged latent

FIG. 132.

Tracings of spontaneous contractions of frog's ventricle, to show refractory period. In each series the surface of the ventricle was stimulated by an induction shock at E, as indicated by the tracing of the signal. In 1, 2, and 3, this stimulus had absolutely no effect, since it fell during the refractory period. In 4, 5, 6, 7, the effect of the shock was to interpolate an extra contraction in the series, the latent period (shaded part) gradually diminishing from 4 to 7 (diastolic rise of irritability). In 8 the irritability of the preparation was already considerable, and the latent period inappreciable. The 'compensatory pause' after the extra beat is also well shown in 4, 5, 6, 7, 8. (Marey.)

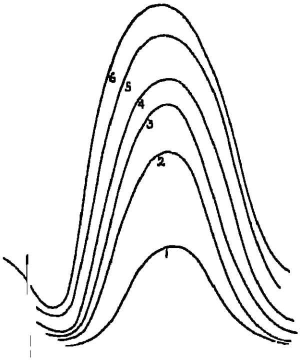
eriod. Just before the next spontaneous contraction the ritability is at its height, and the heart-muscle responds ith a contraction to a minimal stimulus. These facts are ell shown in Fig. 132.

the varying tension of the fibres at the beginning of the contractile process.

Of course if the initial tension be continually increased, w finally arrive at a point at which this peripheral reactiv mechanism gives way; the heart is unable to contract agains the great resistance and becomes permanently stretched an damaged.

The refractory period.—At each contraction of the heart muscle there is a sudden decomposition of contractile material which, so far at least as concerns the incidence of a external stimulus, is maximal, *i.e.* complete. Directly thi has occurred a process of assimilation or re-formatio of contractile material starts. This lasts throughout th

Fig. 131.



Isometric contractions of frog's ventricle The initial tension was continually increased from curve 1 to curve 6, each increase of tension causing a greater energy of contraction (v. Frank)

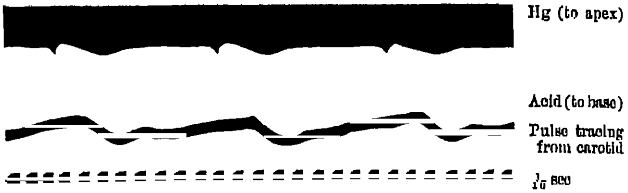
diastolic period, and the store of contractile material is at its maximum just before the next contraction. We may in fact compare the process to a bucket, into which a stream of water is constantly flowing, and which tips up automatically and empties out its contents as soon as the water reaches a certain height. It is evident that the power of the heart-muscle to contract in response to a stimulus (its irritability) must be at a minimum immediately after the automatic discharge, or decomposition, has taken place, and will continually increase from this point as the store of contractile material grows, until it arrives at such a height that the explosive discharge occurs spontaneously. Hence in each cardiac cycle there is a period, known as the refractory

Rhythm of Mammalian Heart

So far as we know, the process of contraction in the mammalian heart is essentially the same as in the frog's heart. The contraction starts in the terminations of the great veins, and travels thence over the auricles. A pause of about one-tenth of a second occurs, and then the ventricles contract, the contraction starting at the base and travelling thence as a wave to the apex.

The wave-like progression of the excitatory condition in the ventricle can be well shown, as in the frog, by leading off the base and apex of the exposed ventricle to the two terminals of a capillary electrometer. We then get in many cases a diphasic variation differing only in the shorter duration of its phases from that described for the frog's heart. We can in fact (as was shown by Waller) by leading off from the apex beat and right hand obtain a photographic record of the variation of the heart in man. Fig. 133 represents the variation of the ventricles as obtained in this way. It will be seen that the variation is triphasic, implying that the excitatory change starting at the base of the heart extends thence to the apex, but the contraction lasts longer at the base than at the apex. The production of the curve is shown by the following diagram (Fig. 134).

Fig 133



Electrical variation of human heart. (Bayliss and Starling)

With a more delicate electrometer it is possible to record also the electrical change due to the auricular contraction. This has the appearance of a sharp spike immediately preceding the triphasic ventricular variation.

The only essential difference between the mammalian and amphibian heart seems to lie in the comparative automaticity of the ventricles in the two cases, the mammalian ventricles possessing much more automatic power than that of the frog. If the ventricles be functionally separated from the auricles by crushing the auriculo-ventricular groove, both parts continue beating, but at different rhythms, the ventricular rhythm being as a rule much slower than that of the auricles. Conduction is probably effected, as in the frog's heart, by the intermediation of the muscular tissue.

FIG. 134

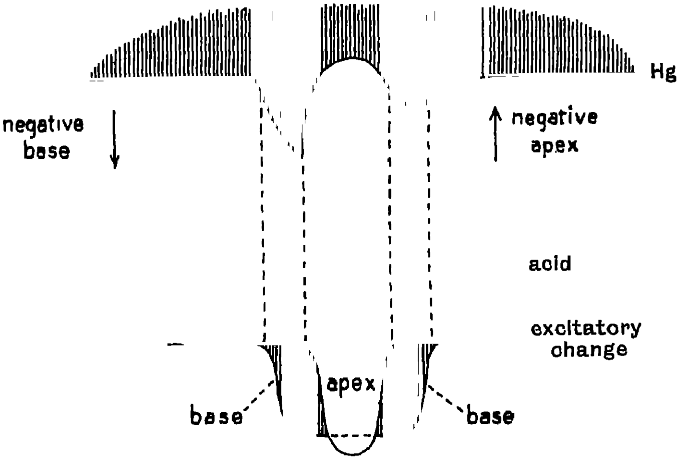


Diagram to show mode of production of electrometer curve in Fig 133 The primary 'negativity' of the base (shaded portion of lower diagram) causes a movement of the Hg meniscus downwards (the acid being connected to the base). Immediately afterwards the negativity spreads to the apex. The whole heart is at same potential, and the meniscus returns sharply. The excited condition then dies away, but lasts longer at the base; hence a second excursion of the meniscus downwards, with a slow recovery.

Although ganglia occur in large numbers in the different parts of the mammalian heart, it is possible to find considerable sections, especially near the apex of the ventricles, which are quite free from ganglion-cells. Porter has shown that such a strip of muscle may be kept alive for some hours by perfusing it through a branch of the coronary artery with defibrinated blood. Under these conditions the strip beats with a regular rhythm, demonstrating the absolute sufficiency of the muscular fibres for the initiation and propagation of the contractile process.

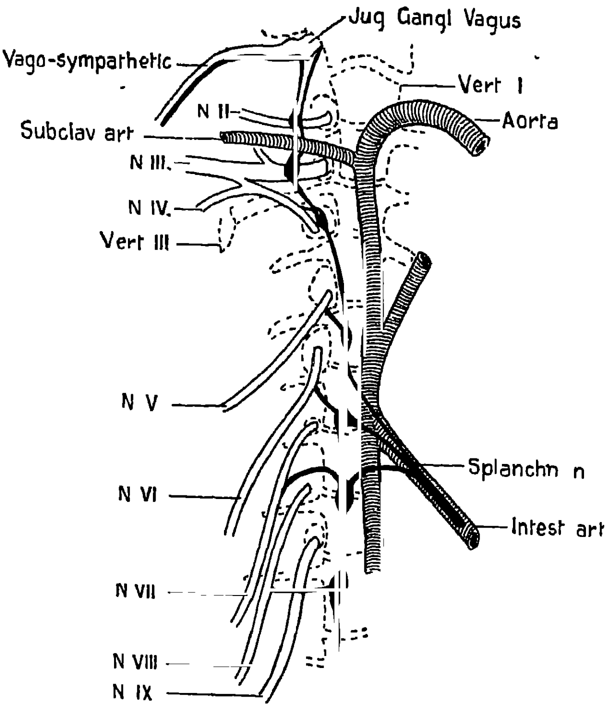
[illegible] in a cardiac cycle

SECTION 5

INNERVATION OF THE HEART

The heart is supplied with nerves from two sources—the vagi and the sympathetic. The fibres supplying the heart run a slightly different course in the frog and in the mammal, such as the dog.

FIG. 135



Sympathetic chain of frog (right side) to show connection with vagus nerve The sympathetic ganglia with their branches are black Of the peripheral branches only the splanchnic nerve is represented (Modified from Ecker)

The sympathetic fibres to the frog's heart leave the cord by the anterior root of the third spinal nerve, pass through the ramus communicans to the corresponding splanchnic ganglion, and thence by the second ganglion, the annulus of

Vieussens, and the first ganglion to the cervical sympathetic. This runs up to join the ganglion trunci vagi, and thence the fibres run down with the vagus nerve (Fig. 135).

Fig 136.

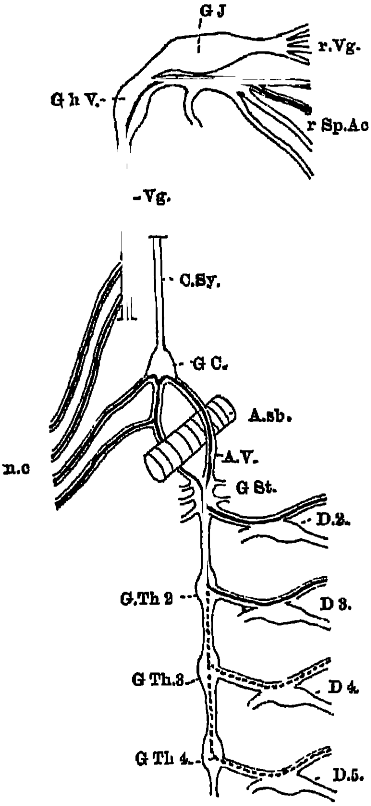


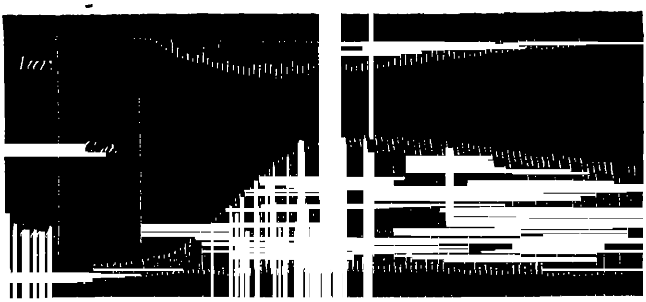
Diagram of cardiac inhibitory and accelerator fibres in the dog (from Foster) r Vg Roots of the vagus. r Sp Ac Roots of the spinal accessory G J Ganglion jugulare G h V Ganglion trunci vagi Vg. Trunk of vagus nerve C.Sy Cervical sympathetic G C Inferior cervical ganglion A V. Annulus of Vieussens A sb Subclavian artery. n c. Cardiac nerves G.St. Ganglion stellatum D 2, D 3, D 4, D 5 Second, third, fourth, and fifth dorsal spinal roots G Th Ganglia of the thoracic chain

In the dog, the sympathetic fibres to the heart leave the spinal cord by the anterior roots of the second and third dorsal nerves, run in the rami communicantes to the stellate ganglion, and thence by the annulus of Vieussens to the inferior cervical ganglion. The cardiac branches containing these fibres run from the stellate ganglion, the annulus, the inferior cervical ganglion, and the trunk of the vagus to the heart.

The accelerator nerves are small medullated fibres as they leave the cord and pass along the anterior roots and white rami communicantes to the stellate ganglion. In this ganglion they end in connection with its cells, and a fresh relay of fibres, which are non-medullated, carries the impulses on to the heart. In the heart they are apparently distributed directly to the muscular fibres, without the intervention of any more ganglion-cell stations.

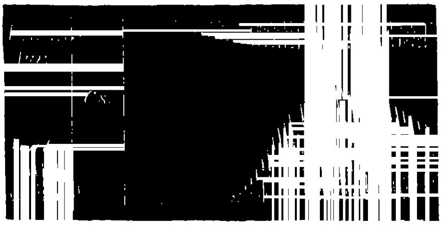
The effect of stimulating these two sets of nerve-fibres is the same in the frog and mammal. In the frog, since the sympathetic fibres run down in the trunk of the vagus, it is necessary, in order to obtain pure effects, to stimulate the intracranial part of the vagus or the cervical sympathetic If the intracranial vagus be stimulated while the heart is beating regularly, the heart stops at once in diastole, or it may give one beat before stopping. If the stimulation be now discontinued, the heart after a little while begins to beat again, at first slowly, and gradually comes back to the normal rhythm. In many cases, if the vagus be stimulated repeatedly, a distinct improving action on the beat is observed, *i.e.* the heart beats more forcibly and rapidly when the stimulation is discontinued

FIG 137



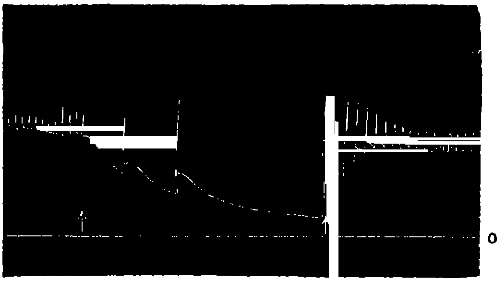
Tracing to show effect of stimulation of the vago-sympathetic nerve on the frog's heart The rhythm is unaltered, but the beats of auricle and ventricle are much decreased in size On ceasing the stimulation the beats become augmented. (Gaskell) than it did at the commencement of the experiment. The vagus is named the inhibitory nerve of the heart. This inhibition may influence either the rhythm or the force of the ventricular contraction, the different results being probably dependent on whether the sinus is most affected, when the beats will be slowed, or the ventricle, in which case each beat will be weaker. If only a weak stimulus be applied to the vagus, the effect may be merely to weaken or slow the beats, without causing a complete stoppage.

FIG. 138.



A tracing similar to Fig. 137. In this case however the stimulation caused complete stoppage (inhibition) of both auricular and ventricular beats. (Gaskell)

FIG 139



Blood-pressure tracing from carotid of dog (taken with Hürthle's manometer), showing effect of excitation of vagus (between the arrows) o. Abscissa line of no pressure.

Stimulation of the sympathetic cardiac nerves has exactly the reverse effect, causing increase in force or rate of the heart-beats or both results at once. They are therefore said to be both augmentor and accelerator nerves.

The augmentor fibres are much less easily tired than the

s. Hence, if the vago-sympathetic of the frog be the first effect is inhibition due to vagus action ; nerve-endings then tiring, the influence of the stimu- the accelerator fibres makes itself apparent, and the t, while stimulation is still going on, commences to beat more rapidly and forcibly than it did before.

Stimulation of the vagus also lowers the conductivity of the cardiac tissue, and, with a carefully graduated stimulus, it is often possible to make a block between auricles and ventricle, so that the latter responds only to every second auricular beat. The accelerator fibres have the reverse effect. We may make an artificial block between auricles and ventricle by clamping rather tightly the auriculo-ventricular groove, so that the ventricle beats only once to every two auricular contractions. If now the accelerator nerves be stimulated the block is removed, and the ventricle beats in normal sequence to the auricles.

These two sets of fibres have exactly the same function in the mammal (dog). Vagus causes slowing of rhythm, depression of force and of conductivity ; accelerators cause acceleration, augmentation, and improvement of conducting power. Since however the beat of the heart is normally ruled by the auricular beat,[1] we find that the action of these nerves is much more pronounced on the auricles than on the ventricles. This is illustrated by the fact that during prolonged vagus excitation the ventricles may begin to beat with a rhythm of their own, while the auricles remain perfectly motionless.

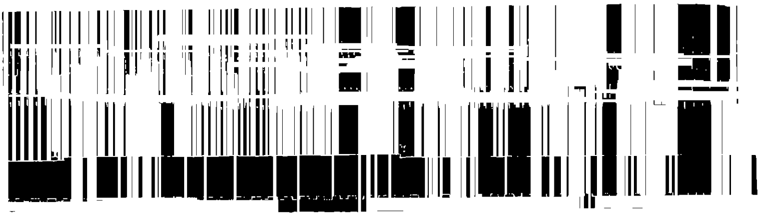
In many animals the vagus centre in the medulla exercises a tonic or continuous inhibitory action on the heart. Thus in the dog, section of one vagus causes a slight quickening of the heart-beat (*e.g.* from 60 to 80 per minute). If now the second vagus be cut, the heart-beat is markedly quickened, and may occur 120 times in the minute. The effect of vagus section is still more marked if the vagus centre in the medulla be in a condition of increased activity, as after administration of morphia, or during asphyxia.

---

[1] The *rate* of the ventricle is determined by the frequency of the excitation arriving at it from the auricles The *strength* of the beat depends on the initial tension of the ventricular muscle, and therefore largely on the amount of blood sent into the ventricle by the auricular contraction

The accelerators are further distinguished from the vagus in the length of their latent period, which in the case of the former is excessively long. The latent period of vagus excitation in the mammal is considerably less than a second, whereas that of the accelerators amounts to ten or even twenty seconds (Fig. 140). The effect of accelerator stimulation lasts for an equal length of time after the stimulation is discontinued.

Fig 140.



Tracings of ventricular (upper curve) and auricular contractions (lower curve) From x to y the accelerator nerves stimulated. Lowest line = seconds

Afferent Nerves of the Heart

Besides these efferent fibres going to the heart, there are other fibres running chiefly in the vagus which serve to carry afferent impulses from the heart to the nervous centres. Some of their terminal branches ramify over the ventricle (of the dog) immediately under the pericardium. We may investigate their functions by stimulation of the central ends of the divided nerves. They may produce one or more of four effects :

1. Pain, as evinced by the movements of an animal not fully under the influence of an anæsthetic (we should be more correct if we said that stimulation of these nerves produced reflex movement).

2. Reflex inhibition of the heart. If one vagus be cut and its central end stimulated, there is very often slowing of the heart by reflex impulses which descend the other vagus.

3 and 4. Pressor and depressor effects. Stimulation of these nerves may cause a reflex raising (pressor) or lowering (depressor) of the blood-pressure.

Cardio-inhibitory Centre

There is one little spot in the medulla, in the neighbourhood of the origin of the vagus nerves, stimulation of which causes inhibition of the heart. If this spot be destroyed, reflex inhibition of the heart can no longer be produced; hence it is spoken of as the cardio-inhibitory centre. The afferent nerves from the abdomen and intestine seem to have very close connections with this centre, so that reflex inhibition of the heart can be easily produced in the frog by tapping a loop of intestine with the handle of a scalpel. This connection explains to some extent the depressed condition of the circulation in man in severe abdominal affections, such as peritonitis.

When the blood-pressure is raised, as by a general constriction of the arterioles of the abdominal viscera, the resistance to the outflow of blood from the heart is increased. This factor by itself would tend to produce a stronger heart-beat, without any accompanying slowing. Under normal conditions however we find that the 'rate of the heart-beat is in inverse ratio to the arterial pressure' ('Marey's Law'), a rise of blood-pressure causing a slowing of the heart, and *vice versâ*. This law holds good only if the vagi are intact. The slowing consequent on rise of pressure is probably conditioned by two factors . (1) the increased pressure in the cranial cavity directly affecting the cardio-inhibitory centre; and (2) the action of the rise of pressure on the endings of the vagus in the walls of the heart, stimulation of these fibres by the increased tension causing a *reflex* inhibition of the heart through the same nerve-trunk. Both these effects would of course be abolished by section of the two vagi.

Influence of Drugs on the Heart

The cardio-inhibitory centre is stimulated by digitaline and morphine, so that the heart is slowed under the influence of these drugs.

Muscarine stimulates the nerve-endings of the vagus. If applied to the frog's heart, it causes gradual weakening and slowing of the beat, and the heart finally stops still in diastole. If a solution of atropine be now applied, the heart commences beating again. It is found that stimulation of the vagus is now absolutely ineffectual in producing inhibition. Hence we argue that atropine paralyses the terminations of the vagus in the heart. The same paralysis of the vagus is produced in the mammal if atropine be injected into the circulation. After administration of atropine, stimulation of the sino-auricular junction (the so-called local inhibitory centre) has no effect on the heart.

If nicotine be injected into the circulation or applied directly to the heart, it first stimulates and then paralyses the nerve cells to which the vagus fibres run, and which give off the inhibitory fibres to the heart muscle. After this drug therefore, although stimulation of the vagus trunk has no inhibitory action (the impulses being blocked in the heart ganglia), stimulation of the sino-auricular junction still causes inhibition in consequence of direct excitation of the post-ganglionic fibres.

Curare has a paralysing influence similar to that of atropine, but only when applied in large doses.

Physostigmin has the same action as muscarine, and, as in this case, its effect is removed by the application of atropine.

Adrenaline, the active principle of the medulla of the suprarenal bodies, when applied directly to the isolated heart, causes a considerable augmentation and strengthening of the beat. When injected into the circulation, it produces a general constriction of the blood-vessels and a consequent rise of blood pressure, and this rise is accompanied by extreme slowing of the heart brought about by stimulation of the vagus centre.

Dilute alkalies (KHO, 1 in 20,000) cause the frog's heart to stand still in a tonic contraction, the tone of the heart gradually increasing till the beats are no longer visible on the tracing.

Dilute acids have the opposite effect, removing the tonic contraction produced by alkalies, and finally causing a stand-still of the heart in complete relaxation.

SECTION 6

THE WORK OF THE HEART

The energy of the ventricular contraction is expended in two ways: firstly, in forcing a certain amount of blood into the already distended aorta against the resistance presented by the arterial blood-pressure, which itself is directly conditioned by the resistance in arterioles and capillaries; and secondly, in imparting to the mass of blood so thrown out a certain velocity. Thus the energy of the muscular contraction is converted partly into potential energy in the form of increased distension of the arterial wall, and partly into the kinetic energy represented by the momentum of the moving column of blood. The work done at each beat may be calculated from the formula:

$$W = QR + \frac{w\,v^2}{2\,g}$$

where W stands for work, w for the weight, and Q for the quantity (volume in ccms.) of blood expelled at each contraction. R is the average arterial resistance or pressure during the outflow of blood from the heart, and v is the velocity of the blood at the root of the aorta. In this equation QR is the work done in overcoming the resistance,[1] and $\frac{w\,v^2}{2\,g}$ is the energy expended in imparting a certain velocity to the blood.

We have already discussed the means whereby the average pressure and velocity of the blood in the aorta may be measured, and it remains only to determine the output of the ventricles at each beat, in order to have at our disposal all the factors necessary for the calculation of the work of the heart. The measurement of the output presents considerable difficulties. Stolnikow and Pawlow practically cut out the systemic circulation altogether, and caused the blood from the left ventricle to traverse an instrument (current-measurer, *Stromaiche*) which recorded automatically the amount of blood that went through it in a given time.

---

[1] This expression QR is only approximately correct Supposing the pressure in the aorta at the beginning of systole is 50 mm Hg and at the end of systole 150 mm, the work could not be deduced accurately from the average pressure, but would need a simple application of the integral calculus for its determination The simple expression employed above deviates from the real value only by about 10 per cent., and is therefore sufficiently accurate for our purpose

In Fig 141, I and II are two cylinders containing accurately fitting floats, bearing writing levers on their upper ends. Each of these communicates below with two tubes, *a* and *v*, one of which is connected to the right carotid artery, while the other is inserted into the superior vena cava All the other branches of the aorta, as well as the inferior vena cava, are ligatured At the beginning of the experiment, cylinder II is filled with defibrinated blood. This blood passes down the tube *2v* into the right auricle, and so through the right ventricle and lungs, where it is aerated, into the left auricle and ventricle. As the heart continues beating, the left ventricle expels its contents into cylinder I, so that the piston in I is rising while that in II is falling. As soon as cylinder II becomes empty, the tubes *1v* and *2a* are released and the tubes *1a* and *2v* are clamped The left ventricle now expels its blood through *2a* into cylinder II while cylinder I is emptying itself through *1v* into the right auricle. We thus get two series of zigzag lines traced by the piston rods, and the frequency of the zigzags is an expression of the output of the left ventricle in a given time.

FIG 141.

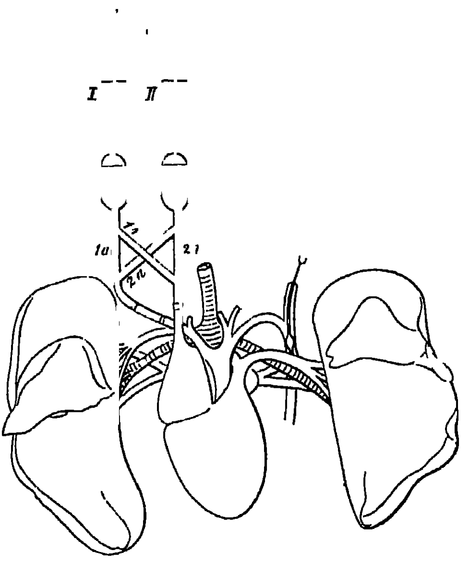


Diagram of Stolnikow's instrument.

This method suffers from the defect that the arterial pressure, in consequence of the absence of external resistance, is extremely low, so that the heart is throughout under highly abnormal conditions. It enjoys however the corresponding advantage that R (the resistance), though low, is constant throughout the experiment, and the work done by the heart is therefore directly proportional to the output.

Better methods are those based upon the application of the plethysmographic method to the heart *in situ.* We may either, as in Tigerstedt's method, employ the pericardium

FIG 142.

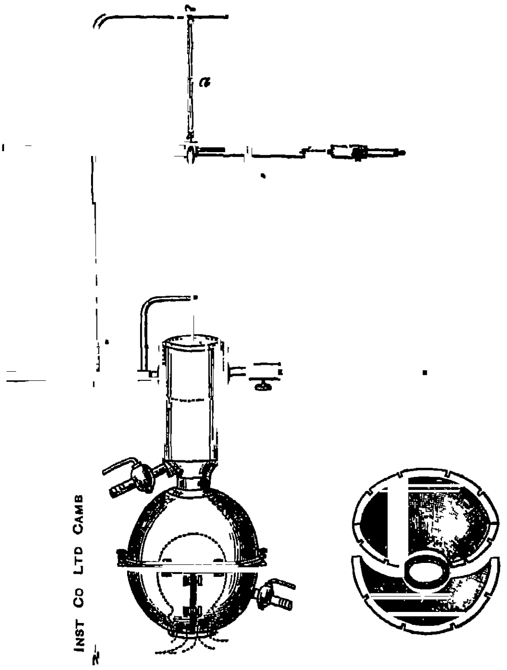


Diagram of Roy's cardiometer On the right of the figure are the two quarter spheres which are clamped on to the pericardium at the root of the heart

itself filled with oil or air as the oncometer, and register the changes in the volume of the heart by connecting the cavity of the pericardium with some form of piston-recorder, or we may make use of Roy's cardiometer. This is a brass sphere in three segments. The two quarter spheres (Fig. 142) are applied round the base of the heart and clamped together, the cut pericardium being attached to their constricted neck. the third segment, a hemisphere, is then applied over the apex of the ventricles and clamped to the parts already *in situ*. Attached to the centre of this hemisphere is a modified piston-recorder, containing a piston working in oil, with which the whole of the apparatus is filled. At *a* is a spring which can be adjusted, so as to exercise a constant pull upon the piston, and reproduce to some extent the negative pressure under which the heart normally works. The piston-rod carries a lever which writes on a blackened surface. The excursions of this lever are proportional to the diminution in volume of the heart at each systole, and therefore serve as a measure of the output of the ventricles.

An attempt has been made to determine the output of the ventricles from the time taken up in the total circulation. It was mentioned earlier that a solution of methylene blue injected into the central end of the jugular vein could be detected in the blood flowing from the peripheral end of the same jugular, after twenty-seven heart-beats. This has been interpreted erroneously as equivalent to saying that the whole blood made the whole circuit of the vascular system and therefore passed through the heart twice in twenty-seven heart-beats. Thus we should have only to divide the quantity of blood in man (5,000 grms. in a man of 65 kilos) by 27, in order to arrive at the output of each ventricle at each cardiac systole, *i.e.* about 185 grms. It is evident however that the figure obtained by the methylene-blue method merely represents the shortest possible time in which any given particle of blood, taking all the short cuts which may be open, can travel round the whole circulation, so that the true output of the left ventricle in man must be considerably less than 185 grms., and is probably not more than one-third of this amount.

From a direct determination by the cardiometer method of the output in animals, Tigerstedt concludes that the output in man at each beat is probably between 50 and 100 ccms. By other methods, Zuntz has come to the conclusion that 60 ccms. represents the average output in man.

Accepting this last figure as correct, we have now all the data for the calculation of the work of the heart.

$QR = 60 \times 0{\cdot}150 \text{ m.} \times 13{\cdot}6$[1] $= 122{\cdot}4$ grammetres.

Taking the velocity imparted to the column of blood in the aorta as $\frac{1}{2}$ metre—

$$\frac{w\,v^2}{2\,g} = \frac{60 \times 0{\cdot}5^2}{2 \times 9{\cdot}8} = 0{\cdot}7 \text{ grammetres}$$

It is evident that this latter factor is negligible, and that for all practical purposes we may regard the work of the heart as proportional to the product of the output and the average arterial blood-pressure.

Taking the average pressure in the pulmonary artery at 25 mm. Hg, the work of the *right* ventricle at each beat would amount to about 20 grammetres, a total for the two ventricles of 140 grammetres per beat, which is equivalent to about 14,000 *kilogrammetres* in the twenty-four hours

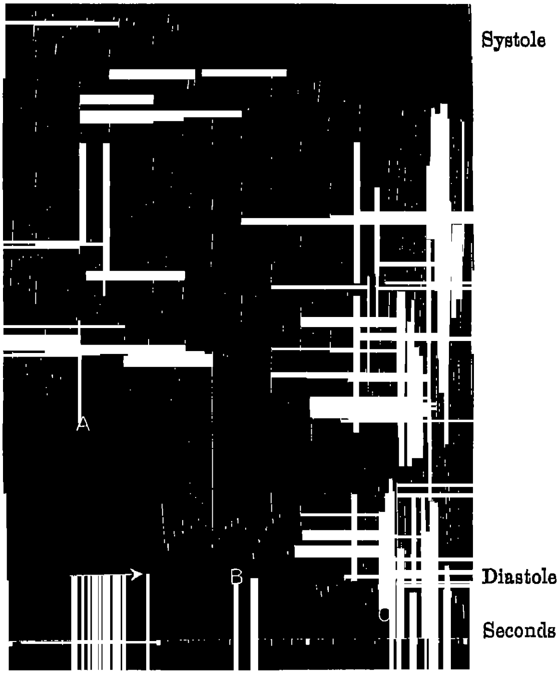
---

[1] The specific gravity of blood is taken here as approximately equal to that of water. If it be desired to allow for this, it would be necessary to divide the product by 1·07.

We are now in a position to discuss the effect of various conditions on the total work of the heart. We have seen that this varies as w × R, so it is evident that any condition which increases either or both of these factors will increase the work done and *vice versa.* Thus on exciting the peripheral end of the vagus, the heart is slowed, the diastole prolonged, and the amount of blood expelled at each systole increased. There is however a fall of mean arterial pressure, and the increased output is not proportional to the diminished frequency of the beat, so that the total output in any given time is less than that occurring before or after the stimulation. R and w being both diminished, the total work done by the heart is lessened.

In dealing however with the effect of experimental or pathological conditions on the work of the heart, it is important to remember the wonderful power of '*compensation*' possessed by this organ. In consequence of the augmentor effect of increased tension on the cardiac muscle, we can increase the resistance to be overcome by the heart to three or four times the normal amount without altering in any way the quantity of blood expelled at each beat. Thus we may put a ligature round the pulmonary artery and gradually tighten it, until the lumen of this vessel is reduced to a third of its normal extent, without causing any material change in the blood-pressure; although, if we connect a manometer with the cavity of the right ventricle, we find that the endocardiac pressure rises to three or four times the normal amount, in order to expel the proper quantity of blood into the pulmonary vessels and so into the left heart. In this case the increased tension acts upon the ventricular muscle during its contraction. The same result is observed if we augment the work thrown on the ventricles by increasing the inflow of blood into them during diastole. This increased diastolic volume of the heart may be brought about either by pressure on the veins of the abdomen, so increasing the venous flow into the heart, or by the injection of large quantities of fluid into the circulation (Fig. 143), or by destroying the aortic valves and allowing regurgitation to take place from the aorta during diastole. In either case, the work done by the ventricles is increased, causing a rise of mean arterial pressure in the first two instances, and preventing any fall of arterial pressure in the last case. A large number of similar experiments may be devised, but they all teach the same lesson, viz. that, within very wide limits, the output of the heart is independent of the resistance to the output.

FIG. 148.



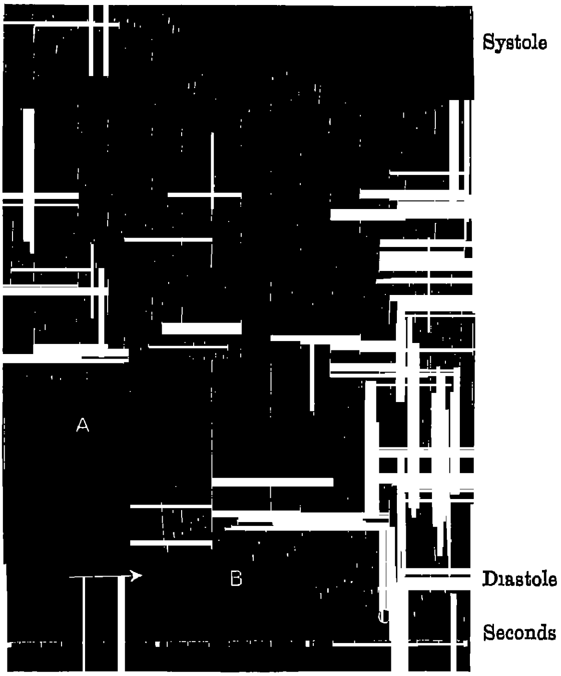
Cardiometer tracing from dog's heart to show effect of increasing the volume of circulating blood (hydræmic plethora) on the total output and the volume of the heart. Between the parts A and B, 30 c c of warm normal salt solution were injected intravenously, and between B and C, 20 c c. more It will be noticed that both the systolic and the diastolic volume are increased, i e. the heart is more distended during diastole, and does not contract to its normal size in systole The contraction volume, and therefore the output, are very largely increased. (Roy)

In a fairly healthy individual, increased work thrown upon the heart by injury or narrowing of the valvular orifices does not necessarily result in fatigue and failure of the heart-muscle, but this tissue may react just as skeletal work of the *right* ventricle at each beat would amount to about 20 grammetres, a total for the two ventricles of 140 grammetres per beat, which is equivalent to about 14,000 *kilogrammetres* in the twenty-four hours

We are now in a position to discuss the effect of various conditions on the total work of the heart. We have seen that this varies as w × R, so it is evident that any condition which increases either or both of these factors will increase the work done and *vice versa.* Thus on exciting the peripheral end of the vagus, the heart is slowed, the diastole prolonged, and the amount of blood expelled at each systole increased. There is however a fall of mean arterial pressure, and the increased output is not proportional to the diminished frequency of the beat, so that the total output in any given time is less than that occurring before or after the stimulation. R and w being both diminished, the total work done by the heart is lessened.

In dealing however with the effect of experimental or pathological conditions on the work of the heart, it is important to remember the wonderful power of '*compensation*' possessed by this organ. In consequence of the augmentor effect of increased tension on the cardiac muscle, we can increase the resistance to be overcome by the heart to three or four times the normal amount without altering in any way the quantity of blood expelled at each beat. Thus we may put a ligature round the pulmonary artery and gradually tighten it, until the lumen of this vessel is reduced to a third of its normal extent, without causing any material change in the blood-pressure; although, if we connect a manometer with the cavity of the right ventricle, we find that the endocardiac pressure rises to three or four times the normal amount, in order to expel the proper quantity of blood into the pulmonary vessels and so into the left heart. In this case the increased tension acts upon the ventricular muscle during its contraction. The same result is observed if we augment the work thrown on the ventricles by increasing the inflow of blood into them during diastole. This increased diastolic volume of the heart may be brought about either by pressure on the veins of the abdomen, so increasing the venous flow into the heart, or by the injection of large quantities of fluid into the circulation (Fig. 143), or by destroying the aortic valves and allowing regurgitation to take place from the aorta during diastole. In either case, the work done by the ventricles is increased, causing a rise of mean arterial pressure in the first two instances, and preventing any fall of arterial pressure in the last case. A large number of similar experiments may be devised, but they all teach the same lesson, viz. that, within very wide limits, the output of the heart is independent of the resistance to the output.

Fig. 148.



Cardiometer tracing from dog's heart to show effect of increasing the volume of circulating blood (hydræmic plethora) on the total output and the volume of the heart. Between the parts A and B, 30 c.c. of warm normal salt solution were injected intravenously, and between B and C, 20 c.c. more. It will be noticed that both the systolic and the diastolic volume are increased, i.e. the heart is more distended during diastole, and does not contract to its normal size in systole. The contraction volume, and therefore the output, are very largely increased. (Roy.)

In a fairly healthy individual, increased work thrown upon the heart by injury or narrowing of the valvular orifices does not necessarily result in fatigue and failure of the heart-muscle, but this tissue may react just as skeletal muscle does to increased work by hypertrophy. Where this hypertrophy is sufficiently developed, we say that the heart-lesion is fully compensated, and such cases may continue for years, without the subject being aware that there is anything the matter with his heart. It is not easy to explain the causation of this hypertrophy, though it is possible that one factor in the increased growth of the tissue-cells may be the increased lymph-flow, which is the result of activity in muscle. The katabolic changes, which accompany activity of muscle, cause a marked rise of osmotic pressure within the muscle-fibres, which therefore swell up in consequence of imbibition of fluid from the surrounding tissue-spaces. Activity thus induces increased supply of nutritive material to the constituent elements of the active tissues.

SECTION 7

INNERVATION OF THE BLOOD-VESSELS

We have already mentioned that the chief resistance to the flow of blood occurs in the arterioles and capillaries. The greater part of this resistance is in the arterioles, and is dependent on the continued contraction or *tone* of their muscular walls. If the spinal cord of a dog be divided just below the medulla, artificial respiration being kept up, the blood-pressure in the carotid artery falls from 120 to 40 mm. of mercury. This fall is not due to any action on the heart, which goes on beating well. It is due to a relaxation of all the arterioles, and also of the portal and perhaps other veins. This relaxation causes a lowering of arterial pressure in two ways. In the first place, the peripheral resistance is largely diminished, and in the second place the total capacity of the vascular system is increased. In consequence of this increase in capacity, we find that section of the cord lowers the pressure, not only in the arteries but also in all the veins of the body.

This experiment shows that the tone of the vessels is dependent on the integrity of their connections with some part of the nervous system. If a section be made just above the medulla, the blood-pressure remains high. If however a certain part of the medulla be destroyed, the blood-pressure sinks as low as if the cervical cord were divided. Stimulation of the same part causes a great rise of blood-pressure, due to increase in peripheral resistance. We learn then that the continued contraction or tone of the small arteries is provided for by a restricted region of the medulla, which we call the vaso-motor centre. (The lower border of this centre is about 4 mm. above the apex of the calamus scriptorius, and its upper border about 4 mm. higher. It apparently coincides in position with the antero-lateral nucleus of Clarke.)

In this section we have to consider the means by which the vaso-motor centre is able to control the calibre of the blood-vessels, and therefore the blood-supply to various parts of the body.

In order to study the influence of the nervous system on the distribution of blood in various parts of the body, it is necessary to determine not only the local condition of the circulation, but also the general blood-pressure; since a diminished flow of blood through any part might be produced either by a local constriction of the blood-vessels, or by a fall of general blood-pressure. It is essential to be certain that any local change which is observed in the circulation is of local production and not a secondary result of vascular constriction or dilatation in some other large area of the body. For the registration of the mean arterial blood-pressure, the mercurial manometer is most advantageously employed.

In order to observe local changes in the circulation, several methods may be adopted.

1. The simplest method is that of ocular inspection. In many cases it is easy to tell by the colour of the organ or part whether its blood-vessels are constricted or dilated. If for instance the abdomen be opened and the splanchnic nerves stimulated, the intestines will be at once observed to become pale and anæmic, owing to this constriction of their vessels.

2. Since the temperature of the peripheral parts of the body is considerably lower than that of the blood flowing into them, it follows that their temperature must be in some degree proportional to the amount of warm blood which reaches them, and we can use the surface temperature of a limb as an index to the changes in the circulation through the limb. Thus if thermometers be tied between the toes of the two hind paws of an animal and the right sciatic nerve be divided, the thermometer on the right side will show a higher temperature than on the left, owing to the vaso-motor paralysis produced in the right leg by the section of the nerve.

3. Changes in the calibre of the blood-vessels of any part will alter the rapidity of the blood-flow through that part, provided that there is no concomitant opposing change in the general blood-pressure. These changes in velocity of the blood might of course be investigated on the arterial side by one of the methods already described. It is more convenient however in most cases to carry out the experiment on the venous outflow, the blood being prevented from coagulating

in the course of the experiment by some artificial means, such as the injection of leech extract, or the defibrination[1] of the circulating blood.

A convenient way of measuring the venous outflow is to let the blood drop on a mica disc attached to a Marey's tambour, from which a tube is carried to a registering tambour. Every drop is recorded on a moving surface by a little elevation of the lever of the registering tambour.

4. The volume of an organ is largely dependent on the amount of blood contained within its vessels. We can therefore judge of the nature of changes in the circulation through an organ by taking a graphic record of its volume. For this purpose we use an instrument known as a plethysmograph or oncometer, of which many forms have been devised.

FIG. 144.

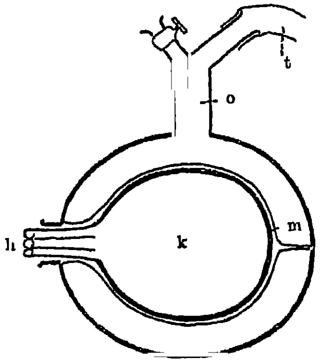


Diagram of oncometer.

Fig. 144 represents diagrammatically the structure of Roy's kidney oncometer. This is a metal capsule, the two halves of which are jointed together, and are accurately fitted to one another except at (h), where a small hole is left for the exit of the kidney vessels and ureters. A delicate animal membrane (m) is attached to the rim of each half of the oncometer, the space between this and the brass capsule being filled with warm oil. The kidney (k) rests inside, supported on the bed of warm oil, from which it is separated by the membrane. The tube (o) leads from the cavity between the brass capsule and membrane to the registering apparatus or oncograph, represented in Fig. 145. Any swelling of the kidney will drive oil out of (o) into the oncograph, and will thus raise the piston of the latter. The excursions of the piston are recorded by the lever (l), which is arranged to write on a blackened surface. Plethysmographs for the limbs and other organs have been constructed on a similar principle.

---

[1] In dogs and cats the blood may be rendered uncoagulable by drawing off half the blood, defibrinating it, and reinjecting it into the circulation. This process is repeated five or six times, when it is found that the blood is no longer coagulable—a condition which lasts for many hours.

Fig. 145.

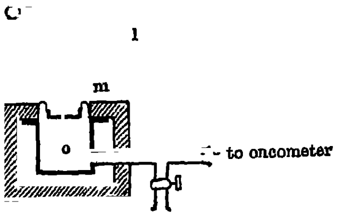


Diagram of oncograph.

Fig. 146.[1]

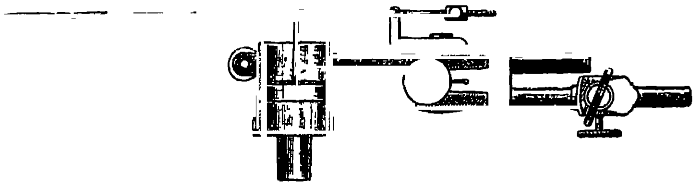
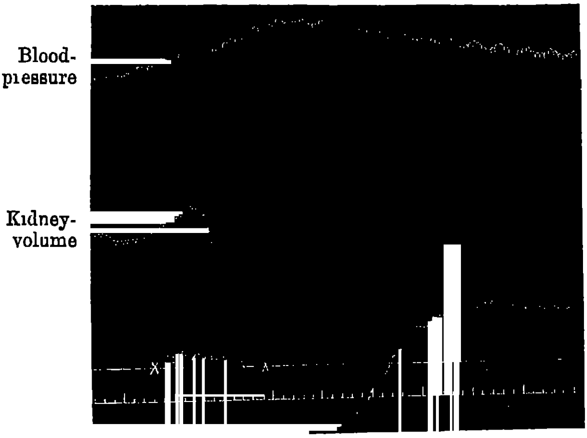


Diagram to show structure of a piston recorder (Hürthle's pattern) This instrument consists of an accurately turned vulcanite piston, moving in a glass cylinder To the piston is attached a light counter-weighted lever The piston moves very easily, has very little tendency to swing on its own account, and gives excursions, which are directly proportional to the changes of volume of air or fluid in the attached oncometer

A very simple form of air-plethysmograph has been devised by Schafer A box is made of vulcanite adapted to the size of the organ whose volume is the object of investigation In one side of the box there is a depression sufficient to accommodate easily the vessels and nerves going to the organ. The oncometer is covered by a glass lid, the connections being made air-tight by means of vaseline A glass tube is fixed in one corner of the box. This is connected by a rubber tube with a piston recorder (Fig. 146) or a tambour Every variation in the volume of the organ causes a movement of air into or out of the oncometer, and thus gives rise to a corresponding movement of the lever of the piston-recorder.

A plethysmograph must always be used in connection with a blood-pressure manometer if we wish to investigate the active condition of the vessels of the organ under consideration. Fig. 147 will serve as an example to show the mode in which these two forms of instruments are employed for the investigation of vascular conditions. The upper curve is the carotid blood-pressure, recorded by means of a mercurial manometer. The lower is the tracing recorded by the lever of an oncograph in connection with an oncometer, in which the kidney of the animal is placed. At the point marked with a cross on the tracing, the peripheral end of the anterior root of the tenth dorsal nerve was stimulated. It will be seen that this stimulation is followed by a slight rise of general blood-pressure, but a marked shrinking of the kidney-volume. The rise of blood-pressure shows us that there must be somewhere a constriction of arterioles giving rise to increased peripheral resistance, since the heart-beat is obviously unaffected. An increased blood-pressure would by itself tend to force more blood into the kidney, and so would cause an expansion of the kidney.

FIG. 147.



Simultaneous tracings of carotid blood-pressure and volume of kidney Between × and × the peripheral end of the divided 10th nerve was stimulated. Time-marking = seconds. (Bradford.)

It is evident that there must be an active contraction of the arterioles of the kidney, emptying this organ of blood, and so causing it to diminish in size. If we had used the oncometer alone, we should have been in doubt whether the shrinking might not be due to failure of the heart's activity. Again, without the oncometer we should only have known that there was increased peripheral resistance in the blood-vessels in some part of the body, but we should not have been able to localise it.

This experiment has taught us already that stimulation of certain nerves causes constriction of the arterioles in definite parts of the body. This influence of nerves on the calibre of the arterioles is still better shown in the ear of the rabbit. If this be held up to the light, the arteries and veins can be plainly seen. If now the sympathetic in the neck be divided, the ear on the same side will instantly become redder and warmer than the other, and on holding it up to the light, all the vessels will be observed to be much dilated, and many small vessels will be evident that could not previously be seen. On stimulating the upper end of the cut sympathetic the reverse effect is produced; the vessels contract, and the ear becomes once more cool and pale. In the same way constriction of the vessels in the web of the frog's foot may be observed under the microscope to follow stimulation of the sciatic nerve. Similar experiments to these have shown that the muscular walls of all the arteries in the body are under the control of the central nervous system, and that they are held in a condition of continued contraction or tone under the influence of the vaso-motor centre. Division of the spinal cord in the neck cuts off the arteries in the trunk and limbs from the vaso-motor centre, and these in consequence become dilated, and the blood-pressure falls. Division of the cord in the dorsal region similarly causes dilatation of the vessels in the lower limbs. If the animal be kept alive after this operation for some time, the vessels recover their tone, but lose it again if the spinal cord be destroyed. We see then that, although the chief vaso-motor centre lies in the medulla, there are also subsidiary centres in the cord, which are able, after a time, to take up by themselves the work of regulating the condition of the blood-vessels in parts of the body supplied by the spinal nerves. The nerves that convey impulses causing constriction of the arteries are called vaso-constrictors or vaso-motors.

Course of the Vaso-constrictor Nerves

In investigating the course of the vaso-constrictor fibres we have to determine

1. The origin of the fibres from the central nervous system;
2. The course of the fibres on their way to their peripheral distribution on the blood-vessels;
3. Their connections with nerve-cells.

The first two details can be found by stimulating various nerves and nerve-roots in different parts of their course and observing the effects produced on the local and general circulation. The importance of the third heading is due to the fact that the vascular nerves, like the visceral nerves generally, do not have their last cell-station in the spinal cord. The fibres carrying vaso-constrictor impulses, which leave the cord, do not pass direct to the blood-vessels, but come to an end in a peripheral collection of ganglion cells, which may belong to the main chain of the sympathetic or be situated more distally and belong to the group of collateral or peripheral ganglia.

These fibres, as they leave the central nervous system, are small medullated nerves. These come to an end in a ganglion, where a fresh relay of fibres starts and carries the impulse on to the muscle-cells of the vessels. These post-ganglionic fibres differ from the pre-ganglionic fibres in being non-medullated.

The discovery of the exact ganglia, with which any given set of nerve-fibres is connected, is rendered easy by the fact that in many animals the sympathetic ganglion-cells are paralysed by nicotin (Langley). The nicotin may be painted on the ganglion or may be injected into the blood-stream. The first effect of the drug is a powerful stimulation of the ganglion-cell, so that, if the drug be injected, there is an enormous rise of blood-pressure owing to the universal vaso-constriction that is produced. This stimulation gives place to a condition of paralysis; the blood-pressure falls below normal owing to the cutting off of the peripheral vascular nerves from the vaso-motor centre. Stimulation of the pre-ganglionic fibre is now without effect, although the normal results follow stimulation of the post-ganglionic non-medullated fibre.

By these methods it has been determined that all the vaso-constrictor nerves of the body leave the spinal cord by the anterior roots of the spinal nerves from the first dorsal to the third or fourth lumbar inclusive. From the roots they pass by the white rami communicantes to the ganglia of the sympathetic chain lying along the front of the vertebral column. Here they take different courses according to their destination.

The fibres to the head and neck leave by the first four thoracic nerves, pass into the sympathetic chain through the ganglion stellatum and ansa Vieussenii to the inferior cervical ganglion, and up the cervical sympathetic trunk to the superior cervical ganglion. Here they end, and the impulses are carried by a fresh relay of fibres, which start from cells in this ganglion and travel as non-medullated fibres on the walls of the carotid artery and its branches.

The constrictors to the fore limb in the dog leave the cord by the white rami of the fourth to the tenth thoracic nerves. The fibres run up the sympathetic chain to the stellate ganglion, where they all end in *synapses* round the cells of this ganglion. The impulses are carried on by non-medullated fibres along the grey rami of the sympathetic to the cervical nerves which make up the brachial plexus, and run down in the branches of this plexus to be distributed to the vessels of the fore limb.

The constrictor impulses to the hind-limb in the dog arise from the nerve-roots between the eleventh dorsal and third lumbar roots All the fibres end in connection with cells in the sixth and seventh lumbar and first and second sacral ganglia of the sympathetic chain, whence the impulses are carried by grey rami to the nerves making up the sacral plexus.

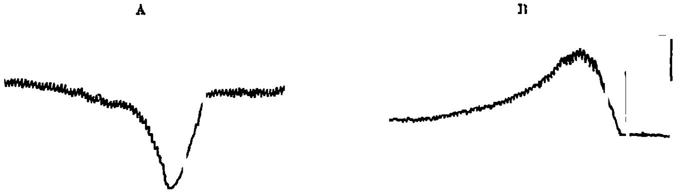
The most important vaso-motor nerve of the body is the *splanchnic nerve.* This nerve receives most of the fibres forming the white rami from the lower seven dorsal and upper two or three lumbar roots, the latter fibres often taking a separate course as the lesser splanchnics. The fibres can be seen to pass through the sympathetic chain of the thorax without interruption and for the most part have their cell-station in the large ganglia, especially the semilunar ganglia, of the solar plexus, whence a thick meshwork of non-medullated fibres is distributed along all the vessels of the abdominal viscera. The area of the vessels innervated by this nerve is so large, that section of this nerve on each side causes a large fall in the general blood-pressure. This fall is more marked in animals such as the rabbit and other herbivora, in which the alimentary canal is proportionately very much developed, and has consequently a very large blood-supply.

Vaso-dilator Nerves

Since the arteries are in a constant condition of moderate contraction, a dilatation might be brought about by a relaxation of this tone by an inhibition of the normal constrictor impulses proceeding to the vessels from the vaso-motor centre. We find however in many parts of the body evidence of the existence of a nerve-supply to blood-vessels antagonistic in its function to the vaso-constrictors. Thus, if the *chorda tympani* nerve going to the submaxillary gland be cut, no change is evident in the blood-vessels of the gland. But if its peripheral end be stimulated, there is instantly free secretion of saliva from the gland, and all the blood-vessels are largely dilated. In consequence of this dilatation the blood rushes through the capillaries so quickly that it has no time to lose much of its oxygen; the blood flowing from the vein is therefore bright arterial in colour, and is increased to six or eight times the previous amount. If atropin be injected into the animal, the action of the chorda tympani on the blood-vessels is unaffected, although the secretion on stimulation is abolished. The chorda tympani is therefore said to contain vaso-dilator fibres for the vessels of the submaxillary gland. Other examples of vaso-dilator (or dilatator) nerves are the *small petrosal* nerve to the parotid gland, the *lingual* nerve to the blood-vessels of the tongue, and the *nervi erigentes* or *pelvic visceral* nerves to those of the penis. It has been thought that all the vessels in the body have a double nerve-supply, vaso-constrictor and vaso-dilator. The presence of the latter variety in a mixed nerve is often difficult to prove, since on ordinary faradic stimulation the constrictor effect is always more pronounced. Moreover the dilators do not seem to conduct any tonic influences to the vessels. Hence, after section of a mixed nerve, the only effect observed is that due to the removal of the tonic constrictor influences, and the vessels in the area of distribution of the nerve are therefore dilated. Two methods however have been made use of to demonstrate the existence of vaso-dilators in a mixed nerve-trunk.

(*a*) If the sciatic nerve be cut, the vessels of the leg and foot dilate. This paralytic dilatation passes off after two or three days, and the vessels resume their normal calibre. If now the peripheral end of the sciatic nerve be stimulated, *dilatation* of the vessels is produced (Fig. 148 B). It seems that the degenerative processes affect the constrictor fibres earlier than the dilator fibres, so that at a certain period after nerve-section the latter alone respond to stimulation.

FIG 148



Nerve freshly divided
Constriction

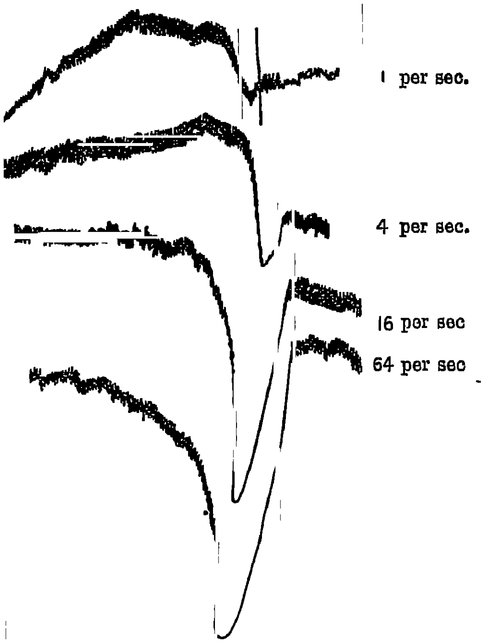
Nerve 4 days degenerated
Dilatation.

Plethysmographic tracing of hind limbs, showing effect of stimulating the sciatic nerve on the volume of the limb, A, immediately after section of the nerve, B, 4 days after section The nerve was stimulated between the two vertical lines Curves to be read *from right to left* (Bowditch and Warren)

(*b*) If a mixed nerve be stimulated with shocks slowly repeated at intervals of one second, instead of with the ordinary faradic current, vaso-dilator effects are often obtained, whereas stimulation of the same nerve with the faradic current produces vaso-constriction (Fig. 149). Thus rapid stimulation of the anterior root of the tenth dorsal nerve in the dog produces shrinking of the kidney from contraction of its blood-vessels. If the same nerve be rhythmically stimulated with single shocks repeated at slow intervals, the kidney swells, showing that its vessels have dilated.

The course of the typical dilator nerves differs very much from that of the constrictors. Instead of leaving the central nervous system in a particular area, and running through the sympathetic chain before proceeding to their destinations, it seems that the dilators may leave the brain or cord by any cerebro-spinal nerve. Thus the chorda tympani springs from the root of the facial nerve, the nervi erigentes from the second and third sacral nerves. All these, however, are probably interrupted in a ganglion or collection of nerve-cells before reaching their destination. Although in some cases, as in the case of the vaso-dilators to the lips and gums of the dog, these cell-stations may be situated in the sympathetic chain (stellate ganglion), in the best marked vaso-dilators, such as the chorda and nervi erigentes, there is no connection at all with the

FIG. 149



Effect on the volume of the hind limbs of the cat of stimulating the sciatic nerve with induction shocks at different rates It will be noticed that with one shock per second, there is hardly any constriction but considerable dilatation, whereas with 64 shocks per second the only effect produced is vaso-constriction. Curves to be read *from right to left* (Bowditch and Warren) main chain of the sympathetic. The nerve-cells of the chorda tympani lie buried in the hilum of the submaxillary gland, while the vaso-dilators of the pelvic nerve are connected with cells in the so-called pelvic ganglion and distributed over the base of the rectum and bladder.

The so-called dilator nerves to the limb vessels seem to be fundamentally different from the typical vaso-dilators just mentioned It has been shown by Bayliss that these nerves have their trophic centre in the spinal root ganglia, and are apparently identical with the afferent nerves of the limbs Mechanical or electrical stimulation of the peripheral end of a cut posterior root, taking part in the formation of a limb plexus, gives rise to well-marked vascular dilatation of the limb vessels, especially those of the skin.

There is a striking analogy between the nerves distributed to the blood-vessels and those going to the heart—which is indeed only a specialised part of the general blood-tubes of the body. These nerves, according to their action on the metabolic activity of the tissues supplied, are divided by Gaskell into *anabolic* and *katabolic* nerves.

The anabolic nerves, as indicated by their name, cause a building up or regeneration of the contractile tissue. They therefore act as inhibitory nerves, and bring about a condition of rest in the tissue. This class of nerves would include the vagus and the vaso-dilator fibres

The katabolic nerves cause an increased activity of the contractile tissue and, as was shown in treating of voluntary muscle (p. 182), active contraction is associated with and derives its energy from a disintegration or katabolism of the complex and unstable muscle molecule (inogen). An ordinary motor nerve to a muscle is therefore a katabolic nerve. This class would include the accelerator nerves to the heart and the vaso-constrictors. The course of these two sets of nerves bears out this comparison, the path taken by the accelerator nerves being identical at first with that of the vaso-constrictor fibres to the head and neck.

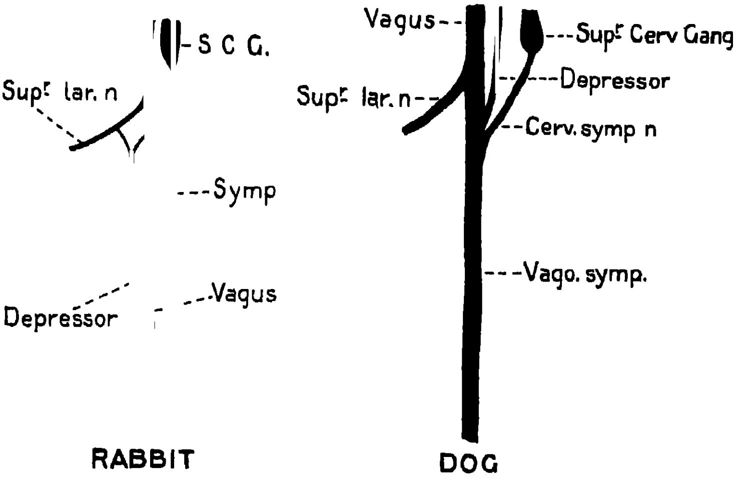
Reflex Alterations of the Blood-vessels

Life is reaction; every vital act is a reaction of the organism to changes in its environment. Hence we have not completed our view of the changes affecting the vessels until we have not only considered the means by which the nervous system acts on the vessels, but also the means by which the centres are excited to action. In fine, we must complete the reflex arc affecting the vessels by considering the afferent impulses to the vaso-motor centre.

The afferent impulses to this centre may be divided into *pressor* and *depressor*; and these names are also applied to the nerves that carry such impulses.

There is in the rabbit, cat, and horse a small nerve in the neck that runs up from the heart to join the vagus or its superior laryngeal branch. If after section of both vagi (to prevent reflex inhibition of the heart) this nerve be cut and its central end stimulated, while the blood-pressure is being registered by means of a mercurial manometer connected with the carotid artery, a marked fall of blood-pressure is at once observed (Fig. 151). This fall of pressure is hardly noticeable after section of the splanchnic nerves, showing that the stimulation of the depressor has affected the vaso-motor centre, inhibiting the constrictor impulses that normally pass down the splanchnic nerves.

FIG. 150

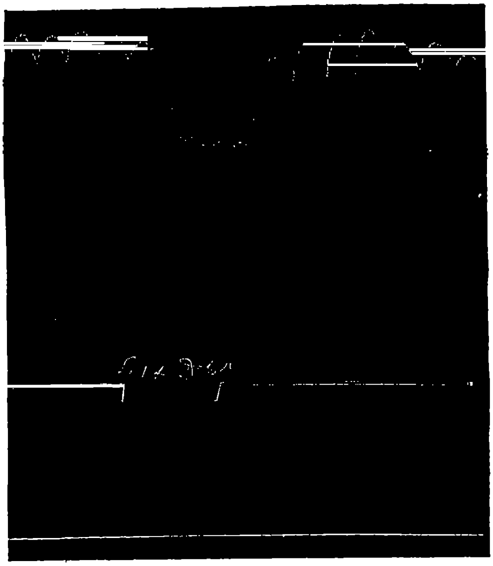


Diagrams of the connections of the depressor nerve in the rabbit and dog, according to Cyon It will be noticed that in the latter animal the depressor nerve runs in the vagus trunk for the greater part of its course

The splanchnic dilatation that is brought about by excitation of the depressor nerve may be demonstrated by enclosing any organ of the abdomen in a plethysmograph. Fig. 152 represents a curve of the splenic volume, and shows the marked expansion, together with fall of general blood-pressure resulting from stimulation of the depressor nerve.

All sensory nerves are *pressor* nerves, *i.e.* stimulation of their central end causes a marked rise of blood-pressure in animals under curare and morphia. Thus a rise of the general blood-pressure follows stimulation of the central end of the cut sciatic or superior laryngeal nerves (Fig. 153). This rise of pressure is due to constriction of the arterioles, especially in the splanchnic area. The effect however of excitation of a purely sensory nerve is not quite so simple as at first appears. In many cases stimulation of the central end of a sensory nerve causes general arterial constriction with a rise of blood-pressure, and at the same time a vaso-dilatation in the area of distribution of the nerve. This can be demonstrated by exciting the central ends of the posterior roots of the nerves to a limb, which causes a swelling of the limb due

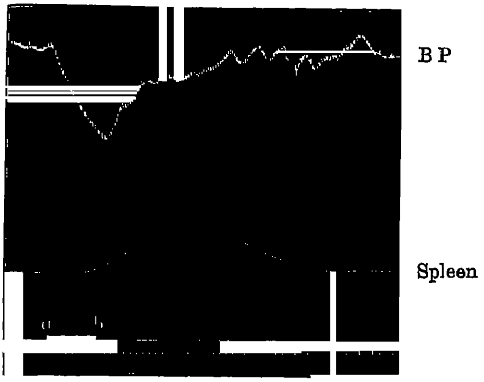
Fig 151



Blood-pressure curve from rabbit showing effect of excitation of central end of depressor nerve (mercurial manometer) (Bayliss.)

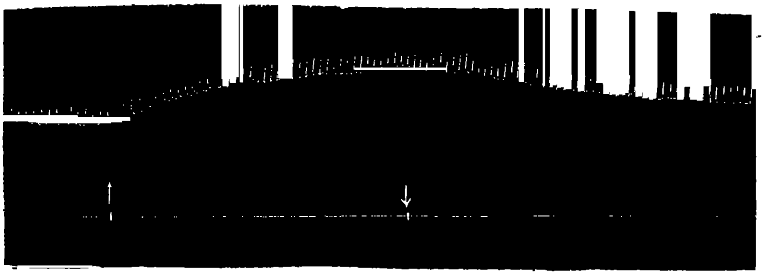
to dilatation of its vessels, accompanied by rise of general blood-pressure owing to constriction of vessels in the splanchnic area and elsewhere. The physiological purpose of this arrangement is obvious. Thus when a limb is injured and inflamed, and a good supply of blood is required for reparative processes, the stimulation of the sensory nerves in the injured area calls forth reflexly a dilatation of the blood-vessels in this area. This dilatation alone allows an increased flow of blood through the part; but this flow is still further increased by

FIG. 152.



Simultaneous tracing of arterial blood-pressure and splenic volume from a rabbit, showing the marked swelling of the spleen associated with fall of general blood-pressure on stimulation of the central end of the depressor nerve. The nerve was excited between *a* and *b* (Bayliss.)

FIG. 153.



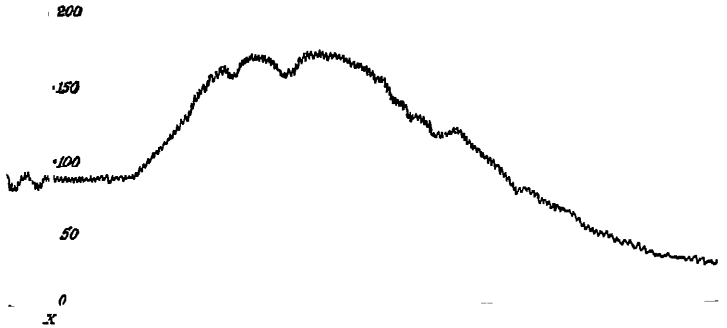
Blood-pressure curve from carotid of dog. Between the arrows the central end of a sensory nerve was stimulated (Hürthle's manometer) the rise of blood-pressure which is caused by the general arterial constriction also induced reflexly by the stimulation of the same nerve.

Factors influencing the Vaso-motor Centre directly. Asphyxia

In addition to its power of response to the effects of peripheral stimuli, the vaso-motor centre in the medulla may also react to changes occurring in the blood with which it is supplied. Thus administration of digitalis or strophanthus to an animal causes a marked rise of general blood-pressure due to the constriction of the peripheral vessels and brought about by impulses from the centre.

The changes occurring in the blood-pressure in asphyxia are important, and depend partly on the abnormal stimulation of the vaso-motor and vagus centres by the venous blood, and partly on the affection of the heart itself. These phenomena are best observed in a curarised animal, and we will first consider them with both vagi cut, in order to shut out the action of the vagus centre. The blood-pressure is registered by means of a mercurial manometer in connection with the carotid artery. On leaving off the artificial respiration, the blood-pressure remains at the same height for twenty or thirty seconds, the only change noticed being the absence of the respiratory oscillations. At this point the blood-pressure suddenly rises rapidly, and in another ten seconds may reach a height twice as great as it was previously. The heart beats a little more forcibly in consequence of the increased cardiac tension, but its frequency is almost unaltered. The blood-pressure remains at this height for about a minute, and then gradually falls, the heart-beats becoming smaller and smaller, until the pressure has sunk to a point very little above the abscissa line (level of no pressure). *This fall in pressure is due to the failure of the heart.* The heart, badly supplied with oxygen, cannot overcome the enormous resistance presented by the contracted arterioles; it gets over-filled, and gradually loses the power of expelling any of its contents. If, when the blood-pressure has sunk to its lowest point, the heart be rapidly cut out of the body, it will at once begin to beat fairly forcibly, being relieved of the excessive internal tension. The vessels however remain constricted until the death of the animal. This is shown by two facts. If, while the pressure is sinking, artificial respiration be recommenced, the heart supplied with oxygen at once begins to beat more forcibly, and the blood-pressure may rise to an even greater height than immediately after the commencement of the asphyxia. Again, if the volume of the kidney be recorded by means of the oncometer, the rise of general blood-pressure produced by asphyxia is seen to be accompanied by a marked shrinking of the kidney, and this shrinking endures until the animal dies, showing that the fall of blood-pressure following the rise is due not to a giving way of the arterial resistance, but solely to a failure of the heart.[1]

Fig. 154



Curve of blood-pressure tracing during asphyxia. The tracing was taken by a manometer connected with the femoral artery of a dog under curare Artificial respiration discontinued at *X* Both vagi had been previously divided

If in the dog, and to a less extent in other animals, the vagi be left intact, the blood-pressure tracing during asphyxia has quite another appearance. At the point of the tracing corresponding to the rapid rise in the previous experiment, there is in this case only a slight rise of pressure, but the heart begins to beat very slowly. At each beat it necessarily the rise of blood-pressure which is caused by the general arterial constriction also induced reflexly by the stimulation of the same nerve.

---

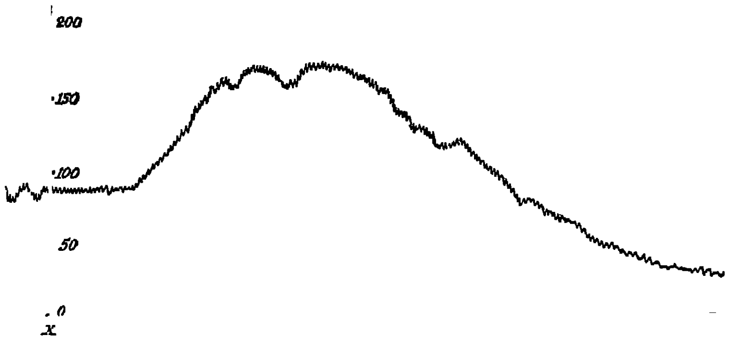
[1] There are no grounds for the statement sometimes made that constriction of the lung arterioles plays any part in this fall of blood-pressure The increased distension of the right side of the heart after asphyxia by ligature of the trachea is due to the thinner walls and greater distensibility of this side of the heart, and to the fact that the forced respiratory movements tend to fill the lung-vessels and the great veins, and so affect chiefly the right heart

Factors influencing the Vaso-motor Centre directly. Asphyxia

In addition to its power of response to the effects of peripheral stimuli, the vaso-motor centre in the medulla may also react to changes occurring in the blood with which it is supplied. Thus administration of digitalis or strophanthus to an animal causes a marked rise of general blood-pressure due to the constriction of the peripheral vessels and brought about by impulses from the centre.

The changes occurring in the blood-pressure in asphyxia are important, and depend partly on the abnormal stimulation of the vaso-motor and vagus centres by the venous blood, and partly on the affection of the heart itself. These phenomena are best observed in a curarised animal, and we will first consider them with both vagi cut, in order to shut out the action of the vagus centre. The blood-pressure is registered by means of a mercurial manometer in connection with the carotid artery. On leaving off the artificial respiration, the blood-pressure remains at the same height for twenty or thirty seconds, the only change noticed being the absence of the respiratory oscillations. At this point the blood-pressure suddenly rises rapidly, and in another ten seconds may reach a height twice as great as it was previously. The heart beats a little more forcibly in consequence of the increased cardiac tension, but its frequency is almost unaltered. The blood-pressure remains at this height for about a minute, and then gradually falls, the heart-beats becoming smaller and smaller, until the pressure has sunk to a point very little above the abscissa line (level of no pressure). *This fall in pressure is due to the failure of the heart.* The heart, badly supplied with oxygen, cannot overcome the enormous resistance presented by the contracted arterioles; it gets over-filled, and gradually loses the power of expelling any of its contents. If, when the blood-pressure has sunk to its lowest point, the heart be rapidly cut out of the body, it will at once begin to beat fairly forcibly, being relieved of the excessive internal tension. The vessels however remain constricted until the death of the animal. This is shown by two facts. If, while the pressure is sinking, artificial respiration be recommenced, the heart supplied with oxygen at once begins to beat more forcibly, and the blood-pressure may rise to an even greater height than immediately after the commencement of the asphyxia. Again, if the volume of the kidney be recorded by means of the oncometer, the rise of general blood-pressure produced by asphyxia is seen to be accompanied by a marked shrinking of the kidney, and this shrinking endures until the animal dies, showing that the fall of blood-pressure following the rise is due not to a giving way of the arterial resistance, but solely to a failure of the heart.[1]

FIG. 154



Curve of blood-pressure tracing during asphyxia The tracing was taken by a manometer connected with the femoral artery of a dog under curare Artificial respiration discontinued at *X* Both vagi had been previously divided.

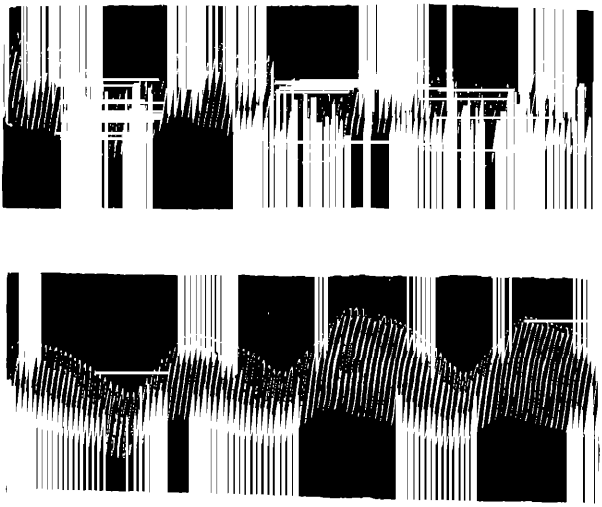
If in the dog, and to a less extent in other animals, the vagi be left intact, the blood-pressure tracing during asphyxia has quite another appearance. At the point of the tracing corresponding to the rapid rise in the previous experiment, there is in this case only a slight rise of pressure, but the heart begins to beat very slowly. At each beat it necessarily sends out a greater volume of blood than when it is beating more frequently, and hence the oscillations on the blood-pressure curve caused by the heart-beats become very large. This slow beat is due to the action of the vagus centre which is excited by the venous blood, and it is at once abolished by section of the two vagi. The sparing of the heart by means of this vagus action enables it to last longer, and the final fatal fall of blood-pressure due to heart failure comes on rather later than when the vagi are divided.

---

[1] There are no grounds for the statement sometimes made that constriction of the lung arterioles plays any part in this fall of blood-pressure The increased distension of the right side of the heart after asphyxia by ligature of the trachea is due to the thinner walls and greater distensibility of this side of the heart, and to the fact that the forced respiratory movements tend to fill the lung-vessels and the great veins, and so affect chiefly the right heart

During the period of increased pressure, waves are often observed on the blood-pressure curve, which must arise in a slow rhythmic variation of the constrictor impulses sent out from the vaso-motor centre. These waves are known as the Traube-Hering curves, and are not to be confused with the waves on an ordinary pressure-curve due to respiration, being much slower in their rhythm than the latter. They are observed not only during asphyxia, but may occur in blood-pressure tracings from normal dogs, and are frequent in dogs poisoned with morphia. Fig. 155 represents tracings obtained from a dog under the influence of morphia and curare. The upper curve, taken while artificial respiration was being carried

Fig. 155.



Blood-pressure tracings showing Traube-Hering curves (C. J Martin) on, shows the three forms of curves—the oscillations due to the heart-beat, next in size those due to the respiratory movements, which in their turn are superposed on the slow prolonged curves, *i.e.* the Traube-Hering curves. The lower curve is taken immediately after cessation of the artificial respiration, and shows only the heart-beats and the Traube-Hering curves.

The presence of Traube-Hering curves may generally be ascribed to a state of abnormal excitation of the vaso-motor centre. This excitation may arise in various ways A very frequent cause is the one just described, viz increased venosity of the blood supplied to the centre Well-marked Traube curves are often observed in cases of hæmorrhage. In spite of the loss of blood, the vaso-motor centre at first maintains a normal arterial blood-pressure by means of vascular constriction. As the bleeding continues, this means becomes inadequate, and at this point the efforts of the centre take on a rhythmic character, giving well-marked Traube curves, just as the arm of a man holding up a weight begins to shake before he is obliged to give way through fatigue. If the bleeding still continues, the pressure sinks steadily and the curves disappear The curves may also be often observed during operations involving exposure of the cord, and may possibly be ascribed in this case to abnormal irritations ascending the posterior columns

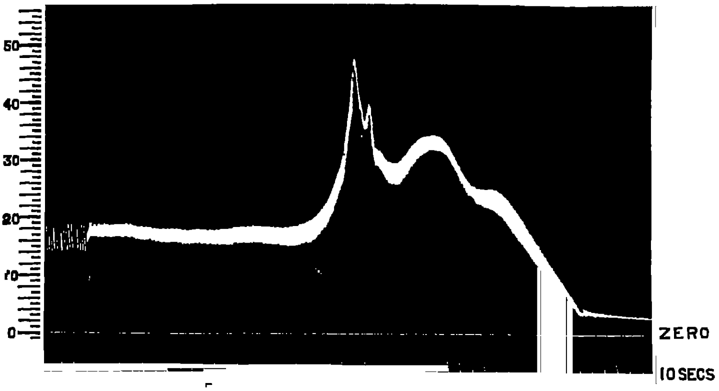
Spinal Vaso-motor Centres

As already mentioned, the spinal cord contains a series of subsidiary vaso-motor centres presiding over the local vascular reactions of the different segments of the body. If an animal be kept alive by means of artificial respiration for some hours after division of the cord just below the medulla, these centres gradually resume their tonic influence, and the blood-pressure slowly rises. If, after two or three hours, artificial respiration be discontinued, the asphyxia excites the centres of the cord, just as it does those of the bulb in the normal animal. The motor discharge reveals itself however in a single prolonged spasm, not in a series of convulsions as is the case when the connections of the bulb are intact. At the same time a universal constriction of the blood-vessels occurs, which outlasts the spasm of the skeletal muscles and causes a very considerable rise of blood-pressure (*v.* Fig. 155A).

Peripheral Vascular Reactions

Even after destruction of all connection with the central nervous system, the blood-vessels still possess considerable powers of maintaining a tone, and adapting themselves to changed conditions. Like all muscular tissues, the arterial wall is largely influenced by tension—increased tension acting as an excitant to increased contraction. Hence increased blood-pressure will cause contraction of the arterial wall, while

FIG 155A



Blood pressure tracing taken by a mercurial manometer from carotid artery of a dog, three hours after section of the cord, just below the medulla oblongata. At o the artificial respiration was discontinued. A general spasm of the skeletal muscles occurred between × and ×. The muscles then relaxed, and were flaccid during the rest of the rise of blood-pressure

diminished blood-pressure will cause relaxation—a state of things eminently adapted to the maintenance of a *continuous* flow of blood through a part, whatever may be the alterations of general blood-pressure conditioned by changes occurring in other parts of the body.

Influence of Gravity upon the Circulation.

In dealing with the mechanics of the circulation we spoke of a mean systemic or general blood-pressure. By this term we imply that the vascular system under normal circumstances is always slightly distended, even if the blood is at rest. The effect of the heart-beat is, by pumping blood from the venous to the arterial side, to depress the pressure in the veins below the mean pressure, and to raise that in the arteries above the mean pressure. On account of the much greater distensibility of the veins, the fall of pressure on the venous side is not nearly as marked as the rise of pressure on the arterial side. This mean systemic pressure probably amounts in the dog to about 10 mm. Hg. It is difficult to measure it with accuracy, owing to the fact that any cessation of the blood-flow, as by stoppage of the heart-beat, will tend indirectly to alter the state of contraction of the blood-vessels, and therefore the tension on the vascular walls.

Owing to the distensibility of the vascular system, the pressure at any part, and the circulation as a whole, must be largely dependent on the influence of gravity. If we take a continuous tube of soft rubber and fill it with fluid to a pressure of 10 mm. Hg., so long as the tube is horizontal the pressure on its walls will be the same throughout its whole circuit. If however the tube be hung up, the weight of the fluid will tend to bulge out the lower dependent parts of the tube, so that the upper part may be entirely collapsed and empty. The vascular system, being also distensible, would behave in a similar manner, if the state of contraction of its walls remained unaltered during changes of position. In man in the upright position the pressure in the femoral artery is 45 mm. Hg. higher than the pressure in the carotid artery. If there is paralysis of the blood-vessels, as occurs during administration of chloroform, or to a lesser degree as the result of illness, this increased pressure in the lower part of the body, including the abdomen, which ensues on change from a horizontal to a vertical position, may cause such a bulging of these vessels that they accommodate the greater part of the blood in the body. An insufficient amount is therefore returned to the heart, and fainting ensues from anæmia of the brain. In the normal individual the effects of change of position are at once compensated for by a change in the distensibility of the vessels, chiefly of the abdomen. These become more rigid in consequence of vaso-constrictor impulses arriving at them from the bulbar centres, and accommodate therefore no more blood than they did in the horizontal position at a lower pressure. If, from any reason, this compensatory action of the vaso-motor centre is imperfectly carried out, the brain is insufficiently supplied with blood and the respiratory centre is also set into increased activity. The increased respiratory movements thus set up act as a respiratory pump, the contractions of the diaphragm, alternating with strong expiratory contractions of the abdominal muscles, serving to support the yielding abdominal vessels and to drive their contents on into the heart.

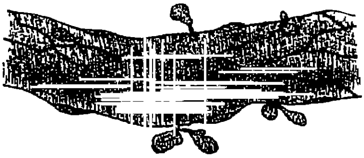
SECTION 8

THE CAPILLARY CIRCULATION

The capillaries may be regarded as the chief part of the circulation, since the whole object of the varied arrangements of the heart and arterioles is to secure an adequate flow of blood through these smallest vessels—that is, a supply of blood adequate to the needs of the tissues in which the capillaries are embedded. The transudation of lymph and the chemical interchange between the tissues and the blood take place only in the region of the capillaries and small veins. At present we have no evidence of an influence of the nervous system on the calibre of the capillaries, or on the interchange taking place between them and the surrounding tissues, although the circulation here is indirectly affected by changes induced in the calibre of the arterioles.

The condition of the endothelial wall of the capillaries and its influence on the blood-stream seem to be chiefly dependent on the nutrition of the surrounding tissues. This is well exemplified in the series of phenomena classed under the head of *inflammation.* By inflammation we understand those processes wherein the organism reacts to a destructive lesion of its tissues ; and these processes in the higher animals are connected with marked vascular changes, which can be well studied on the tongue of the frog. If this be spread out and arranged for microscopical observation, a beautiful picture of the normal circulation of the blood through the arterioles, capillaries, and veins is afforded. As a destructive lesion to call forth inflammatory changes, a small piece of the tongue may be cut off, or the tongue may be painted with a very weak solution of croton oil. The following series of phenomena are then observed. At first the injury is followed by a dilatation of all the vessels, consequent upon dilatation of the arterioles , the blood rushes through the capillaries, and many vessels make their appearance which were before invisible. After a time, the vessels still remaining dilated, the stream of blood becomes slower, and it is then seen that in the small veins there are two layers : a layer next the vessel wall, in which large numbers of leucocytes are present, and which remains almost stationary; and an inner layer of slowly moving red corpuscles. Since this slowing of the circulation is unattended by any narrowing of the calibre of the vessels, it must be due to an increased friction between the blood-plasma and its contents and the capillary wall. It has been explained by saying that the layer of endothelium is more adhesive. In the capillaries the endothelium is also thickly covered with leucocytes, but here the red corpuscles are mixed with the leucocytes, and there is not such a division into two layers as in the veins. Very soon, at one or two spots, it will be observed that a leucocyte is squeezing itself or being squeezed through the capillary wall, so that half of it lies inside, half of it outside the vessels, and the emigration speedily becomes complete. This emigration of white blood-corpuscles increases in extent, and at the end of seven or eight hours the tissues in the immediate neighbourhood of the small veins and capillaries are infiltrated with masses of leucocytes. At the same time the amount of lymph that transudes through the vessel-walls is largely increased, so that it cannot be carried off quickly enough by the lymphatics, and remains in the interstices of the tissues, causing a swelling or *œdema*.

FIG 156



Emigration of leucocytes through capillary wall. (Arnold.)

The true significance of this process of inflammation has been pointed out in recent years by Metchnikoff. This observer has shown that all the vascular phenomena of inflammation are directed towards furthering the emigration of leucocytes, and that these leucocytes, or *phagocytes*, have the power of devouring the irritant body if it be a micro-organism, or of removing the tissues killed by the lesion, and so clearing the ground for a regeneration of the tissue. It is probable that the ingestion of micro-organisms is often preceded by the secretion of some material from, *e.g.* the eosinophile cells, which kill the bacteria or prepare them in some way for their ingestion. Such a condition of phagocytosis—that is a collection of wandering cells to devour and remove disintegrated tissues, foreign bodies, or micro-organisms—has been shown to occur in all animals, even in those destitute of a vascular system. The animals with such a system have the advantage over the lower animals, in that the circulating blood is always bringing up fresh relays of leucocytes to vanquish and destroy the offending body. In many cases the chemical or microbic influence destroying the tissues is too powerful for the leucocytes to overcome; they also are destroyed, and the dead leucocytes collect in the tissues and form pus. If the leucocytes are successful in removing the irritant body, they disappear, perhaps wandering back into the blood-stream, and the lost tissue is replaced by regeneration of the surrounding tissues.

SECTION 9

VARIATIONS IN THE QUANTITY OF BLOOD

From a few observations on executed criminals it has been determined that the amount of blood in the human body forms about one-thirteenth of the body-weight. Thus a man weighing 65 kilos would have about 5 kilos of blood in his vessels.

The determination of the total blood is carried out in the following way A small sample of blood is taken and diluted one hundred times with distilled water. The animal is then bled to death, the blood defibrinated, and the vessels washed out with water, until the outflowing fluid is no longer tinged with hæmoglobin. The organs very rich in blood, such as the liver and spleen, are minced and washed free from hæmoglobin All the blood and the washings are then mixed together, and diluted with water until the tint of the mixture is exactly identical with that of the first sample. We then have only to divide the total volume by 100 to arrive at the amount of blood contained in the animal's vessels

A method has been devised by Haldane by means of which the total volume of blood can be determined in the living subject The animal or man experimented on is made to breathe in and out of a bag containing a measured quantity of CO gas, mixed with pure oxygen The expired air is allowed to pass through soda lime on its way back to the bag in order to absorb the carbon dioxide, and fresh oxygen is supplied from a reservoir as that in the bag is used up. When the oxygen has displaced all the CO gas into the lungs, the bag is disconnected, and a sample of blood taken, the relative amounts of CO-hæmoglobin and of oxyhæmoglobin being determined by a colorimetric method. The *amount* of CO-hæmoglobin can be estimated from the amount of CO absorbed in the course of the experiment, and since the proportion of CO-hæmoglobin to total hæmoglobin has been also determined, it is easy to calculate the total amount of hæmoglobin in the body.

A determination of the relative content of the blood in hæmoglobin now enables us to calculate the total mass of blood. Estimations carried out in this way by Haldane and L. Smith led to the conclusion that the amount of blood in the body is not $\frac{1}{13}$ as generally assumed, but less, varying in different individuals from $\frac{1}{16}$ to $\frac{1}{30}$, the average being $\frac{1}{20.5}$

Plethora and Hydræmic Plethora

The effects of increasing the total volume of circulating fluid may be studied by injecting several hundred cubic centimetres of defibrinated blood or normal saline fluid into a vein. In the latter case, since the blood is rendered more dilute, the condition is called hydræmic plethora.

On the arterial pressure the result of such an injection is not very marked. There is a slight initial increase in the pressure, but the increase is by no means proportional to the amount of fluid injected, showing that the fluid is not to any large extent contained in the arterial system. On examining the pressure in the veins however we find a very great relative rise of pressure, and on opening the abdomen it is seen that all the veins are distended and that the liver is swollen. The effect of increasing the volume of circulating fluid would be to increase the mean systemic pressure, and therefore one would expect to find a large increase both in arterial and venous systems. But the organism prevents the rise on the arterial side by relaxing the whole system of arterioles, so that the distribution of pressures is altered, and the venous approximates more closely to the arterial pressure. This arterial dilatation however augments the velocity of the blood: it has been found that the velocity may be accelerated to six or eight times the normal rate by injecting an amount of salt solution equivalent to 50 per cent. of the total blood.

The high venous pressure causes increased diastolic filling of the heart, and therefore augments both strength and frequency of the beat. Thus the work of the heart is increased in three ways, viz. by:—

(1) Rise of arterial pressure.
(2) Greater frequency of beat.
(3) Increased output at each beat (Fig. 143).

These series of changes result however in the relief of the vascular system. The heightened pressure in the abdominal veins and capillaries causes a great leakage of fluid in the form of lymph from the capillaries of the intestines and liver, while the increased pressure and velocity of the blood in the glomeruli of the kidney induce a copious secretion of urine, so that within a couple of hours after the injection of salt solution the volume of the circulating fluid may have returned to normal.

This recovery is effected with greater difficulty if the plethora has been brought about by the injection of defibrinated blood, since this fluid cannot escape rapidly from the capillaries, nor can it be excreted unchanged by the kidneys. Hence it is easy to kill an animal by wearing out its heart, if too large quantities of defibrinated blood be injected. The ultimate fate of the injected blood is to be used as food by the tissues, and to be eliminated by the ordinary channels.

It must be remembered that the blood serum of one animal is often poisonous for the corpuscles of another. Thus a few c c of dog's serum injected into the peritoneal cavity of a rabbit will cause death This poisonous action is also shown by mixing dog's serum with defibrinated rabbit's blood, in which case the red corpuscles of the latter are broken up, setting free hæmoglobin (*hæmolysis*)

The Effects of Hæmorrhage. Anæmia

Any diminution of the total volume of the blood, as by bleeding, would tend to lower the pressure on both sides of the system. The vaso-motor centre however strives to maintain a normal arterial pressure, and so the circulation through the brain unaltered. This object is carried out by a general vascular constriction, which diminishes the total capacity of the system and alters the distribution of pressure throughout the system, tending to keep the blood as much as possible on the arterial side. Thus a slight loss of blood has no influence on the arterial blood-pressure, but causes a fall of pressure in the veins, blanching of the abdominal organs, and diminished flow of urine. The heart beats very frequently, and so aids in emptying the venous into the arterial system.

The deficiency of circulating fluid caused by bleeding is soon remedied by a transfer of fluid from the tissues to the blood. This transfer is independent of the flow of lymph from the thoracic duct into the blood, and is the direct consequence of the universal fall of capillary pressure which results from the bleeding. The abstraction of fluid from the tissues is responsible for the extreme thirst which is the result of hæmorrhage, and which directs the animal to take up by the alimentary canal the fluid which is wanting to the body.

This transfer of fluid from tissues to blood is extremely rapid; even during the course of a bleeding it is found that the later samples of blood are more dilute than those obtained at the beginning.

This mechanism suffices only to make up the supply of circulating fluid. After a bleeding however an animal has lost proteids and blood-corpuscles, and these constituents of the blood are but slowly restored, the former directly from the food, the latter by an increased activity of the blood-forming cells in the red marrow.

CHAPTER VII

LYMPH AND TISSUE-FLUIDS

In no part of the body does the blood come in actual contact with the living cells of the tissue. In all parts the blood flows in capillaries with definite walls consisting of a single layer of cells, and is thus separated from the tissue-elements by these walls and by a varying thickness of tissue. In some organs, such as the liver and lung, every cell is in contact with the outer surface of some capillary; while in others, such as cartilage (which is quite avascular), a considerable thickness of tissue may separate any given cell from the nearest capillary. A middleman is thus needed between the blood and the tissues, and this middleman is the *lymph* which fills spaces between all the tissue-elements, so that any tissue can be regarded as a sponge soaked with lymph.

Throughout these spaces we find a close network of vessels lined, and separated from the tissue spaces, by a layer of extremely thin endothelial cells, and this plexus communicates with definite channels—lymphatics, by which any excess of fluid in the part is drained off. The lymphatics all run towards the chest, where those of the limbs join a large vessel (the receptaculum chyli), which carries the lymph from the alimentary canal, to form the thoracic duct. This runs up on the left side of the œsophagus, to open into the great veins at the junction of the left internal jugular with the subclavian vein. A small vessel on the right side drains the lymph from the right upper extremity and right side of the chest and neck.

The lymph may be looked upon as a part of the plasma which exudes through the capillary wall, bathes all the tissue-elements, passes between the endothelial cells into the peripheral lymphatic network, whence it is carried by lymphatic trunks into the thoracic duct, by which it is returned again to the blood.

It is easy to obtain lymph for examination by putting a cannula (a small tube of glass or metal) into the thoracic duct, and collecting the fluid that drops from it in a glass vessel.

We may also tap in a similar way one of the large lymphatic trunks of the limbs; but in the latter case we have to use artificial means to induce a flow of lymph, since little or none can be obtained in a normal animal from a limb at rest; the only part of the body, where there is normally a constant flow of lymph, being the alimentary canal. And thus we cannot regard the flow of lymph from a part as any index of the chemical changes going on at that part. In a limb at rest foodstuffs are being taken up from the blood and being burnt up by the muscles with the production of CO_2, although we may not be able to obtain a drop of lymph from a cannula in one of the lymphatics.

The lymph is thus truly a middleman; as any substance, oxygen or foodstuff, is taken up by a tissue-cell from the lymph surrounding it, this latter recoups itself at once at the expense of the blood.

Thus there would seem to be no need for lymphatics to drain the limb, were it not that under many conditions which we shall study directly, the exudation of lymph from the blood-vessels is so excessive that, if it were not carried off at once and restored to the blood, it would accumulate in the tissue-spaces, give rise to dropsy, and by pressure on the cells and blood-vessels affect them injuriously.

PROPERTIES OF LYMPH

Lymph obtained from the thoracic duct of an animal varies in composition and appearance according to the condition of the animal, whether recently fed or fasting. From a fasting animal the lymph is a transparent liquid, generally slightly yellowish, and sometimes reddish from admixture of blood-corpuscles. When obtained from an animal shortly after a meal, it is milky from the presence of minute particles of fat that have been absorbed from the alimentary canal. In the latter case, if the intestines be exposed, the small lymphatics are to be seen as white lines running from the intestine to the attached part of the mesentery. It is owing to this fact that these lymphatics have received the special name *lacteals*, the lymph in them being called the *chyle*. The fatty particles form the *molecular basis* of the chyle.

On microscopic examination the transparent lymph of fasting animals presents colourless corpuscles similar to those of blood, or perhaps we ought to say identical, since the leucocytes of the blood are probably derived from the corpuscles that have entered with the lymph through the thoracic duct.

All the lymphatics pass at some point of their course through lymphatic glands, which we may look upon as factories of leucocytes, since these are much more numerous in the lymph after it has traversed the gland than before. Leucocytes are also formed in all the numerous localities where we find adenoid tissue, such as the tonsils, air passages, alimentary canal (Peyer's patches and solitary follicles), Malpighian bodies of the spleen, and thymus.

The lymph is alkaline, has a sp. gr. of about 1015, and clots at a variable time after it has left the vessels, forming a colourless clot of fibrin, just like blood-plasma. It contains about 6 per cent. of solid matters; the proteins consisting of fibrinogen, paraglobulin, and serum albumen. The salts are similar to those of the liquor sanguinis, and are present in the same proportions.

THE PRODUCTION OF LYMPH

Many physiologists have thought that, in the transudation of the fluid which forms the lymph, there is an active intervention on the part of the endothelial cells composing the capillary wall, and that lymph is therefore to be regarded as a true secretion. A careful investigation of the known experimental facts has failed to show that the endothelial cells act otherwise than passively, as filtering membranes of variable permeability. The factors which are responsible for the transudation of lymph may be divided into two classes—mechanical and chemical, the former depending largely on the pressure of the blood in the vessels, and the latter chiefly on the metabolism of the cells outside the vessels.

According to the views here laid down, the formation of lymph may be compared to a process of filtration. If this view is correct, the amount of lymph formed in any given capillary area must be dependent on the difference of pressure between the blood in the vessels and the fluid in the extravascular tissue-spaces. This latter pressure is normally extremely low, so that in attempting to test the truth of this view, we must try the effects of altering the pressure inside the vessels, in the expectation of finding that the lymph production will rise and fall as the capillary pressure is increased or diminished. On attempting to carry out such experiments in different parts of the body, we have to recognise another factor besides the capillary pressure, viz. the permeability of the vessel-wall. Whereas the capillary walls in the limbs and connective tissues generally present a very considerable resistance to the filtration of lymph through them, and keep back the larger portion of the proteins of the blood-plasma, the intestinal capillaries are much more permeable, giving at moderate capillary pressures a continual flow of lymph and separating off only a small proportion of the proteins. It is in the liver however that we find the greatest permeability. Here a very small pressure suffices to produce a great transudation of lymph, containing practically the same amount of protein as the blood-plasma from which it is formed.

The ease with which fluid passes out from the capillaries of the liver is probably due to the fact that these vessels, unlike most other capillaries of the body, have not a complete endothelial lining Thus it is impossible to display a continuous endothelial lining by means of silver nitrate. The cells surrounding the capillaries are large and branched, and possess marked phagocytic powers, so that after an injection of carmine granules or bacteria into the blood stream these bodies are found in quantity within the cells Owing to the incompleteness of this investment, the liver cells in many places abut on the lumen of the capillary On injecting the blood system of the liver, the injection is found to run with ease into channels situated within the cells themselves, and it is reasonable to conclude that the blood plasma takes the same course through these intracellular channels, by which it passes into the lymphatics which lie at the periphery of the lobules

In experiments on the lymph production in the limbs alterations of capillary pressure have but slight effect. The lymph-flow from a limb lymphatic is practically unaltered by changes in its arterial supply, although a definite increase may be obtained by ligaturing all the veins of the limb so as to cause a very great rise of capillary pressure The lymph-flow from the intestines can be measured by collecting the lymph from the thoracic duct. If the lymphatics which leave the liver in the portal fissure be previously ligatured, the whole of the thoracic duct lymph in an animal at rest is derived from the intestines. It will be found that lowering of the capillary pressure in these organs by obstructing the thoracic aorta stops the flow of lymph absolutely, whereas a rise of capillary pressure, such as that produced by ligature of the portal vein, causes a four- or five-fold increase of the lymph.

The effect of rise of capillary pressure on the lymph-flow is still more striking in the case of the liver. If the inferior vena cava be obstructed just above the opening of the hepatic veins, there is a great fall of arterial pressure, but, owing to the damming back of the blood, a rise of pressure in the liver capillaries to three or four times the normal amount. This rise causes an enormous increase in the lymph-flow from the thoracic duct. The lymph may be increased eight to ten times in amount, and it contains more protein than before. If the portal lymphatics be previously ligatured, obstruction of the inferior cava has no effect on the lymph-flow, showing that the whole of this increase is derived from the one region of the body where the capillary pressure is increased, viz. the liver.

We must conclude that in those regions of the body where the capillaries are fairly permeable, the most important factor in the lymph production is the intracapillary pressure.

In the case of the limbs and connective tissues generally, the pressure factor is probably, under normal conditions, of less importance, so that the second condition, the chemical, comes here more into prominence. The capillary wall not only permits of filtration under certain pressures, but also allows the passage of water and dissolved substances by diffusion and osmosis. These osmotic interchanges between blood and cell through the intermediation of the lymph are constantly going on in the normal life of the tissue, and are quite independent of the amount of lymph produced. Thus a gland-cell may use up oxygen, calcium, or sugar, and create a vacuum of these substances in the layer of lymph immediately surrounding the cell. There is at once a disturbance of the equlibrium, and a flow of these substances from blood to lymph is set up. In consequence of the wonderful arrangements in the tissues for ensuring the intimate contact of blood and lymph without intermingling, these changes can occur with great rapidity. We find, for instance, that if a very large amount (40 grms.) of dextrose be injected into the circulation, osmotic equilibrium between blood and lymph is established within half a minute of the termination of the injection. In this case the rise of osmotic pressure[1] caused by the injection of the sugar attracts water from the lymph, and this in its turn from the tissue-cells, until the osmotic pressure inside and outside the vessels is the same. By this means the volume of the circulating blood is increased at the expense of the tissues. A process of this character may however work under normal circumstances in the reverse direction, and lead to a passage of fluid from blood to tissues and tissue-spaces. Every active contraction of a muscle, for instance, is attended by the breaking down of a few large molecules into a number of smaller ones, and this increase in the number of molecules causes a rise of osmotic pressure in the muscle-fibre and surrounding lymph, and therefore a passage of fluid from blood to lymph. In the same way a cell of the submaxillary gland, when stimulated by means of its nerve, pours out a quantity of fluid into the gland-duct, and so into the mouth. This fluid comes in the

FIG 157

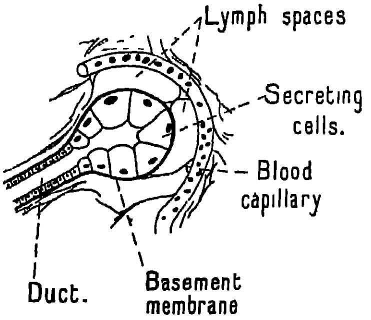


Diagram to show relation of the secreting cells of a gland to the blood and lymph supply.

---

[1] A fuller description of the phenomena of osmotic pressure will be found in Chapter X.

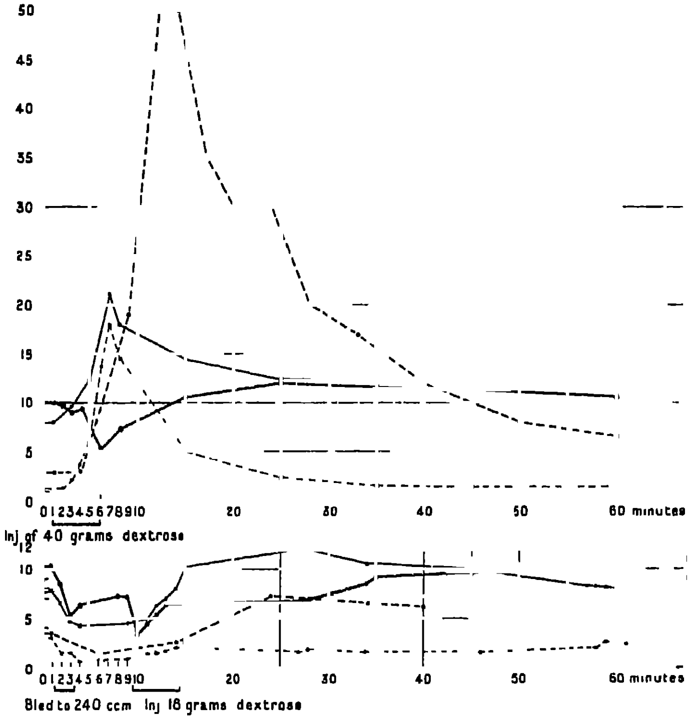
first instance from the cell itself, but the cell recoups itself from the surrounding lymph, raising the concentration of this fluid, and the difference in concentration thus caused at once induces a passage of water from blood to lymph (Fig. 157). Hence salivary secretion is associated with a large flow of fluid through the capillary walls of the gland. In this passage the endothelial cells of the capillaries play no part, the whole process being conditioned by changes in the extravascular gland-cell. We have only to paralyse the gland-cell by means of atropin in order to see that the active flushing of the gland which accompanies activity produces merely a minimal increase in the lymph-flow from the gland.

The influence of tissue-activity in the production of lymph is still better shown in the case of a large gland, such as the liver. Stimulation of this organ by the injection of bile salts into the blood-stream causes a large increase in the lymph-flow from the organ, and therefore in the lymph-flow from the thoracic duct.

It is important to remember that the relative insusceptibility of the limb capillaries to pressure holds only for the absolutely normal capillary. Any factor which leads to impaired nutrition of the vascular wall, such as deficiency of supply of blood or oxygen, the presence of poisons in the blood or in the surrounding tissues, scalding or freezing, increases at the same time its permeability. Under such conditions the limb capillary reacts to changes of pressure like a liver capillary, the slightest increase of pressure causing an appreciable increase in the lymph production. This increased lymph production may be too great to be carried off by the lymphatic channels, so that the exuded fluid stays in the tissue-spaces, distending them and causing the condition known as œdema or dropsy.

Lymphagogues.—Among the substances which have a direct action on the vessel wall are a number of bodies which were described by Heidenhain as lymphagogues of the first class. As their name implies, these bodies on injection into the blood-stream cause an increased flow of lymph from the thoracic duct. They may be extracted from the dried tissues of crayfish, mussels, or leeches by simple boiling with water. Commercial peptone has a similar effect. Heidenhain regarded these bodies as direct excitants of the secretory activities of the endothelial cells. They are however general poisons, having a special action on the vascular system, and their effect on the lymph production is probably due simply to their

Fig. 158.



Curves to show the influence of intravenous injection of dextrose on the arterial and venous pressures and on the flow of lymph from the thoracic duct The upper diagram represents the effect of the injection of dextrose in a normal animal, *i e* rise of arterial and venous pressures, and large increase in lymph. The lower curve shows the effect of injecting dextrose after a preliminary bleeding In this case the fluid attracted into the vessels by the sugar only just suffices to make up for that lost in the bleeding. Hence the venous and arterial pressures are little altered from normal, and there is very little increase in the lymph flow.

In both diagrams—
Thick continuous line = arterial blood-pressure in cm Hg
Thin ,, ,, = portal ,, in cm water.
Thin dotted line = vena cava ,, ,, ,,
Thick ,, = lymph-flow in c c. per ten minutes.

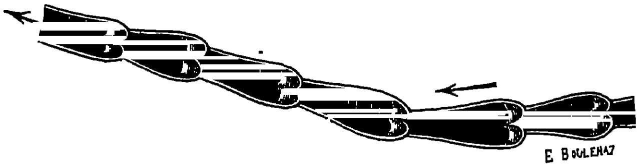
deleterious action on the capillary wall. Although these bodies act chiefly on the liver capillaries, so that the main increase in the thoracic duct lymph is derived from the liver, they can be shown also to have some effect in the same direction on the intestinal and skin capillaries. In fact the injection or ingestion of these bodies often gives rise to a copious eruption of nettle-rash, *i.e.* swellings of the skin due to an increased exudation of lymph into the meshes of the cutis.

An increased lymph-flow from the thoracic duct may be produced also by the injection of large amounts (10 to 40 grms.) of innocuous crystalloids such as dextrose, urea, or sodium chloride into the circulation. In this case the lymph becomes much more dilute. The explanation of the action of these bodies is very simple. We have already seen that injection of large amounts of dextrose into the circulating blood raises the osmotic pressure of this fluid. The blood therefore imbibes water from the tissues and swells up, *i.e.* a condition of hydræmic plethora is brought about as surely as if several hundred cubic centimetres of normal salt solution were injected into the circulation. This increase in the total volume of the blood causes a rise of pressure throughout the vascular system,—arteries, capillaries, and veins,—and the increased capillary pressure combined with the watery condition of the blood induces a great transudation of lymph, especially in the abdominal organs. The lymph is more watery because the blood also is diluted. That the action of these bodies is purely mechanical is shown by the fact that, if the rise of capillary pressure be prevented by bleeding the animal immediately before the injection, the increase in the lymph-flow is also prevented (Fig. 158, p. 293), although the concentration of the sugar or salt in the blood is still greater than in the experiments in which bleeding was not performed.

MOVEMENT OF LYMPH

In the frog the circulation of lymph is maintained by rhythmically contracting muscular sacs, which are placed in the course of the main lymph-channels, and pump the lymph into the veins. In the higher animals and in man, the onward flow of lymph is effected partly by the pressure at which it is secreted from the capillaries into the interstices of the tissues, but also to a large extent by the contractions of the skeletal muscles. In the smaller lymph-radicles the pressure of lymph may attain 8 to 10 mm. soda solution. In the thoracic duct, at the point where it opens into the great veins of the neck, the pressure is obviously the same as in these veins, that is to say, from −4 to 0 mm. Hg, the negative pressure being occasioned by the aspiration of the thorax. This difference of pressure is sufficient to cause a certain amount of flow. It must be remembered however that under normal circumstances no lymph at all flows from a resting limb. The only part of the body which gives a continuous stream of lymph during rest is the alimentary canal, the lymph in which is poured out into the lacteals, and thence makes its way through the thoracic duct. Movement, active or passive, of the limbs at once causes a flow of lymph from them. Since the lymphatics are all provided with valves (Fig. 159), the effect of external pressure on them is to cause the lymph to flow in one direction only, *i.e.* towards the thoracic duct and great veins. Hence we may look upon muscular exertion as the greatest factor in the circulation of lymph. The flow of lymph from the commencement of the thoracic duct in the abdominal cavity to the main part of it in the thoracic cavity is materially aided by the respiratory movements; since, with every inspiration, the lacteals and abdominal part of the duct are subjected to a positive pressure, and the intrathoracic part of the duct to a negative pressure, so that lymph is continually being sucked into the latter.

FIG 159.



A lymphatic vessel laid open to show arrangement of the valves. (Testut)

THE ABSORPTION OF LYMPH AND TISSUE-FLUIDS

On injecting a coloured solution or suspension into the connective tissues of any part of the body, and gently kneading the part, it is found that the fluid fills all the lymphatic channels running from the part; and we can in this way inject the lymphatics of the limb and trace their course on to the thoracic duct. The same path is taken by micro-organisms as they spread in the tissues, or by particles of carmine or Indian ink which have been introduced in tattooing. It is on account of these facts that the lymphatics are often spoken of as the absorbent system.

This process of lymphatic absorption is however a slow one, unless aided to a large extent by passive or active movements of the surrounding parts, and cannot therefore account for the rapid symptoms of poisoning which supervene within two or three minutes after the hypodermic injection of a solution of strychnine or other poison. That this absorption is not dependent on the lymphatics is shown by the fact that the symptoms occur almost as quickly, when all the tissues of the limb have been severed with the exception of the main artery and vein. In the same way, after injecting methylene blue or indigo carmine into the pleural cavity or subcutaneous tissues, the dye-stuff appears in the urine long before any trace of colour can be perceived in the lymph flowing from the thoracic duct. The absorption in these cases is by the blood-vessels, and consists in an interchange between blood and extravascular fluids, apparently dependent entirely upon processes of diffusion between these two fluids. So long as any difference in composition exists between the intra- and extra-vascular fluids, so long will diffusion-currents be set up, tending to equalise this difference.

More difficulty is presented by the question of the mechanism of absorption by the blood-vessels of the normal tissue-fluids—such an absorption as we have seen to occur after loss of blood by hæmorrhage. It seems probable however that this absorption depends on the small proportion of protein contained in the tissue-fluid as compared with the blood-plasma. If blood-serum be placed in a bell-shaped vessel (the mouth of which is closed by a gelatinous membrane which does not permit the passage of protein), and suspended in normal salt solution, it is found that the serum absorbs the salt solution until the manometer attached to the bell-jar indicates a pressure of 25-30 mm. Hg. Thus we may conceive that there is normally a balance in the capillaries between the processes of exudation and of absorption, the former being conditioned by the capillary blood-pressure and the latter by the difference in protein content, and therefore of osmotic pressure between the blood-plasma and tissue-lymph. A rise of capillary pressure will upset this balance in favour of transudation and the blood will become more concentrated, whereas a fall of pressure will turn the scale in favour of absorption and the volume of blood will be increased at the expense of the tissue-fluids.

THE PART PLAYED BY THE LYMPH IN THE NUTRITION OF THE TISSUES

The fact that the tissue-cells are separated by the lymph and the capillary wall from the blood shows that in all interchanges between the blood and tissues, the lymph must act as the medium of communication. The lymph-flow however plays very little part in this process. The muscles of a resting limb are taking up nourishment as well as oxygen from the blood and giving off their waste products—carbonic acid and ammonia, though not a drop of lymph may flow from a cannula placed in a lymphatic trunk of the limb. In fact the interchange of material between tissue-cell and blood through the mediation of the lymph is carried out in the same way as are the gaseous interchanges, viz. by a process of diffusion. This explanation however holds good only for the diffusible constituents of the blood and will not account for the supply of the indiffusible protein molecules to the cell. Apparently the only way in which the tissues can obtain their supply of protein is from the small proportion of this substance which has filtered through the vessel-wall into the lymph. The increased exudation of concentrated lymph to the tissues which occurs in inflammatory conditions or as the result of injury is therefore of advantage, since it furnishes an abundant supply of protein food to be used up in the regeneration of the damaged cells.

CHAPTER VIII · 298-376

✓THE MECHANISMS OF DIGESTION

Section 1

GENERAL CHARACTERS OF THE PROCESSES OF DIGESTION

We have already mentioned that the cells derived from the hypoblast of the embryo, and lining the inner surface of the tube from which the body is formed, are alimentary in function, *i.e.* they have the office of taking up the various foodstuffs and converting them into a form suitable for assimilation by the other tissues of the body. In some of the lower animals the cells lining the alimentary canal devour the food particles in the same manner that the amœba does, secreting around them, after ingestion, a fluid which seems to dissolve them. In the higher Vertebrates this process is simplified, in that the cells lining the canal are differentiated into those that secrete a fluid capable of dissolving foodstuffs, and those which have the duty of absorbing the foodstuffs that have been rendered soluble by the action of the digestive fluids. The secreting cells are collected together in depressions or outgrowths of the epithelial lining of the alimentary canal to form glands; and the secretions in different parts of the canal have different properties, some being adapted to rendering soluble the starchy constituents of food, while the action of others is limited to proteins.

During the time that the food is in the mouth it is acted upon by the mixed secretions of the parotid, submaxillary, and sublingual salivary glands. And here we find the chief digestive action consists in the conversion of insoluble starch into soluble dextrins and sugar.

In the stomach the food is acted on by the gastric juice, the secretion of a number of simple tubular glands with which the mucous membrane is thickly set. Its chief action is on the proteins, hydrating these and converting them into albumoses and peptones. In the duodenum the food is acted on by the pancreatic juice and the bile, the secretion of the liver. The former has a digestive influence on all three classes of foodstuffs, converting starch into sugar, proteins into peptones, and splitting up neutral fats with the formation of glycerin and free fatty acids. In the small and large intestine the mucous membrane is thickly set with a number of simple tubular glands, which are called Lieberkühn's follicles. These secrete an alkaline juice, which has only slight digestive powers. It contains invert ferments which convert cane-sugar into lævulose and dextrose, and maltose into dextrose, and also a ferment, *erepsin*, which has the property of causing a complete hydrolysis of the albumoses and peptones already formed by the agency of gastric and pancreatic juices, and converting them into amino-acids and bases.

Pro.. hyd. Small Sr

FERMENTS.—All the digestive juices owe their powers to the presence in them of certain ferments; and we may take the opportunity of saying a few words with regard to ferment action in general. Ferments enter or are said to enter into most of the physiological processes of the body. To a ferment has been ascribed a prominent part in the coagulation of the blood; and we shall meet with them later on in considering the functions of the liver and kidney. But it is in digestion that these bodies play the most important part. In all the changes that are effected by their agency there is the conversion of a body of high potential energy into one with less potential energy; and this conversion is in most cases associated with hydrolysis, *i.e.* the original body is combined with one or more molecules of water to form the new substance of lower potential energy.

In inquiring into the nature of ferments we are met at the outset with the difficulty that probably no one has ever prepared a pure ferment; so that we can only study their properties by studying those of the fluids or precipitates presumed to contain a ferment from the fact that they can give rise to certain changes in other substances. First, as to the conditions of their activity. A ferment such as diastase can convert an indefinite amount of starch into sugar, provided that the product of its activity (*i.e.* the sugar) be not allowed to accumulate in too large a quantity. Thus by increasing the strength of a ferment solution we do not increase the amount of substance it is able to transform, but merely the rapidity of its action.

The exact effect of increasing the amount of ferment varies according to the nature of the ferment in question Thus in some cases, as with diastase, the rapidity of change of the starch is in direct proportion to the amount of ferment present. If a given solution takes four minutes to convert a starch solution to the 'achromic' point (*i.e* the stage at which no coloration is given with iodine), a ferment solution of double the strength will take only two minutes to effect the same change In the case of other ferments, such as pepsin and trypsin, it is necessary to increase the concentration of the ferment four times in order to double the rate of change produced

A ferment is active only within certain limits of temperature; and for each ferment there is a certain optimum temperature at which its activity is greatest. This, for the ferments met with in the body, is between 40° and 45° C. For the diastase of malt it is between 60° and 65° C. At a temperature of 0° the activity of all ferments that occur in warm-blooded animals is indefinitely checked, although it has been shown that the pepsin or gastric ferment of fishes still preserves some power at this temperature. At 65° C. all ferments met with in the body are destroyed, and do not recover on cooling.

They are soluble in distilled water, and precipitated from their solutions by alcohol. The digestive ferments are precipitated by saturation of their solutions with ammonium sulphate. This method has been used for obtaining them in a state approaching purity, and they have been found to have the general composition of proteins. The amount that can be collected however is so small that it is impossible to make an accurate study of their properties, and even then we do not know whether the substance we have represents the pure ferment, or is merely a protein to which the ferment is intimately adherent.

A ferment is therefore a body which can effect changes in a surrounding fluid of certain bodies of high potential energy into bodies of more stable composition with an evolution of kinetic energy in the form of heat, without itself being used up in the process.

It has long been known that the action of a ferment was impeded and finally checked by the accumulation of the products of its activity in the solution. Thus diastase added to a strong solution of starch will convert a certain amount of it into maltose, but the process will cease before the whole of the starch is so converted. If now the solution be diluted, or the maltose removed by dialysis, the action will recommence. In this respect the reaction exactly resembles those known in chemistry as reversible reactions.

The question arises whether a ferment action can also be reversible. An answer to this question has been supplied by Croft Hill in the affirmative. The inverting ferment, *maltase*, contained in yeast and in the succus entericus, converts maltose into dextrose If however the ferment be allowed to act on strong solutions of dextrose, it converts a small proportion of this back into maltose. The changes in the two cases are as follows:

$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$$
$$2C_6H_{12}O_6 = C_{12}H_{22}O_{11} + H_2O$$

This observation is of importance as showing that synthetic changes can occur in the body apart from any activity of cells, provided only that the right conditions are present. It is evident that, if the sugar were contained in a vessel whose walls were permeable to or had a distinct affinity for maltose, so that this was removed as fast as it was formed, the ferment that normally converts maltose into dextrose (a downward change) might convert the whole of the dextrose into maltose.

The changes brought about by ferments can in most cases be also effected by very simple means, such as heating with water under pressure or warming with dilute acids. The changes are in nearly all cases *hydrolytic*, the original substance taking up water, and splitting into simple substances. In this process the ferment adds neither to the products of the reaction nor to the energy evolved in the reaction. The only factor altered by the ferment is the *velocity* of the reaction. Cane-sugar in the presence of water is slowly inverted into lævulose and dextrose If a little mineral acid be present, or some *invertin* be added, the reaction takes place within a few minutes.

The nature of ferment action may be better conceived if we compare it with certain changes that have long been known in inorganic chemistry, and are spoken of as katalytic changes. Thus nitrogen trichloride may be made to explode by contact with various substances, such as phosphorus or oil. In its explosion it splits up into free nitrogen and chlorine—molecules which are more stable, and have therefore less potential energy, than those of the original nitrogen trichloride. In the manufacture of sulphuric acid, nitric oxide is used as a carrier of oxygen from the atmosphere to the sulphur dioxide produced by the burning of sulphur. Thus:

$$\underset{\text{Nitric oxide}}{NO} + O = \underset{\text{Nitrogen tetroxide}}{NO_2}.$$

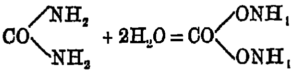
$$\underset{\text{Sulphur dioxide}}{SO_2} + NO_2 + H_2O = \underset{\text{Sulphuric acid}}{H_2SO_4} + \underset{\text{Nitric oxide}}{NO}.$$

In this case we have at the end of the reaction the same amount of nitric oxide that we started with, and it would be theoretically possible, by using a small quantity of nitric oxide as oxygen-carrier, to convert an indefinite amount of sulphur dioxide into sulphuric acid. Since in this reaction we know the exact chemical processes that go on, the word 'katalysis' is not used. On the other hand, we employ this word in speaking of the splitting up of hydrogen peroxide by means of spongy platinum into water and oxygen:

$$\underset{\text{Hydrogen peroxide}}{2H_2O_2} = 2H_2O + O_2.$$

But the difference is probably merely one of degree. The substance which acts katalytically exercises an attraction on one of the atoms in the unstable molecule, which is sufficient to give the impetus to its decomposition, although not leading to an actual combination of the two, as in the case of the nitric oxide quoted above. So we may suppose that the invert ferment, for instance, combines with a molecule of water, and passes it on to the cane-sugar, or it may be that it merely exercises an attraction on some of the constituents of the cane-sugar molecule, so increasing its tendency to break up and unite with the surrounding molecules of water, with the evolution of heat and the production of the more stable bodies, lævulose and dextrose.

The ferments which play so important a part in the digestive functions belong to the class of *unorganised* ferments. The term 'ferment' has been applied to another class of bodies, which are distinguished as the *organised* ferments. These are living organisms which have the power of inducing definite changes in the media in which they live. This faculty is intimately bound up with the life of these organisms. Destruction of this by the action of small amounts of chloroform, or by subjecting them for some time to the action of absolute alcohol, irrevocably destroys their fermentative properties. With the organised as with the unorganised ferments there is a change of the affected substance from a condition of high to one of lower potential energy. The changes induced however are often much more than a mere hydrolysis. The yeast fungus, for instance, converts sugar into alcohol. In this process it has been thought that the change represents the metabolism of the organism itself. But it is becoming more and more difficult to draw a hard and fast line between the two kinds of action. The ammoniacal fermentation of urine depends on the presence of a micro-organism, the *Micrococcus ureæ*, which converts urea into ammonium carbonate.



$$CO\begin{cases}NH_2\\NH_2\end{cases} + 2H_2O = CO\begin{cases}ONH_4\\ONH_4\end{cases}$$

Urea Ammonium carbonate

This action is stopped by antiseptics. It is possible however to kill the micro-organisms and extract from the dead cells an unorganised ferment which has exactly the same effect. In the same way it has been shown that, if yeast cells be thoroughly broken up and pressed, an unorganised juice is obtained which converts dextrose into alcohol. In fact the organised ferments seem to act by ferments enclosed within their constituent cells, whereas the unorganised ferments are formed by living cells and excreted so as to act outside the cell.

Recent research tends more and more to enhance the significance of these ferment-like bodies, which acting in infinitesimal quantities are able to exert so important an influence on the direction and velocity of chemical reactions.

In the alimentary canal the following ferments are found:—

Ptyalin (saliva); *amylopsin* (pancreatic juice). Starch to maltose.

Invertin. Cane-sugar to invert sugar (dextrose and lævulose).

Lactase. Lactose to dextrose and galactose.

Maltase. Maltose to dextrose.

Pepsin. Proteins to albumoses and peptones.

Trypsin. Proteins to peptones, amino-acids, etc.

Erepsin. Albumoses and peptones to amino-acids and hexone bases.

Steapsin. Neutral fats to fatty acids and glycerin.

Rennin. Caseinogen to casein.

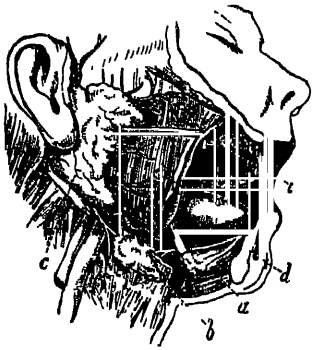
A whole array of bodies of this class are moreover found in the cells and body-fluids under normal and pathological conditions, *e.g.* toxins and antitoxins, coagulins and hæmolysins with their 'anti' bodies, oxydases, etc.; and it seems not improbable that all chemical processes of cells may in time be reduced to ferment actions, the functions of the living protoplasm being confined to the determination of the direction of the process at any moment.

SECTION 2

SALIVARY DIGESTION

The *saliva* is a mixture of the secretions of the submaxillary, sublingual, parotid, and small mucous and serous glands of the buccal cavity (Fig. 160). It has a low specific gravity, 1002 to 1009; it is slightly alkaline, and slimy from the presence of mucin. On microscopic examination it is seen to contain epithelial scales and 'salivary corpuscles'—small round cells with granular contents, which are probably leucocytes escaped from the tonsils. It consists of—

FIG. 160



Dissection to display the salivary glands *a*, sublingual gland; *b*, submaxillary gland; *c*, parotid gland; *d*, common opening of ducts of submaxillary and sublingual glands, *i*, opening of duct of parotid gland

Water.

Salts, especially potassium and sodium chlorides.

Traces of albumen.

Mucin.

A diastatic ferment (ptyalin).

Occasional traces of potassium sulphocyanide.

Gases, especially carbon dioxide, with traces of oxygen and nitrogen.

The amount of saliva secreted in twenty-four hours varies from one-half to two litres. The greater part is re-absorbed in the alimentary canal.

ACTION OF THE SALIVA ON THE FOOD

Saliva chiefly serves to moisten foodstuffs, and so aid in mastication and deglutition. This is indeed in carnivora its sole function. In herbivora and man it exercises a digestive action on starch by virtue of the ptyalin it contains. If some saliva be added to some boiled starch in a test-tube, and the mixture be kept at 35° C. for some time, the starch is gradually converted into a mixture of maltose and dextrin. The first stages of this conversion are extremely rapid, as is shown by the fact that if a warm decoction of starch be taken into the mouth, kept there for 15 to 30 seconds, and then ejected, the coloration with iodine has entirely disappeared, all the starch having in this short time been converted into dextrin and maltose. The stages of the process are as follows:

1. Starch, opalescent solution, blue with iodine.

2. Soluble starch, clear solution, blue with iodine.

3. A mixture of dextrins, erythro- and achroodextrin. The former with iodine gives a mahogany-red colour.

4. Maltose and achroodextrin, the erythrodextrin being converted into maltose, while some of the achroodextrin remains unaffected. The liquid now reduces Fehling's solution by means of the maltose it contains, and gives no coloration with iodine. Addition of large excess of absolute alcohol gives a white precipitate of achroodextrin. This ferment action is dependent on temperature, is most active at about 40° C., and is finally abolished at about 60° C. It can only take place in a neutral or slightly alkaline medium, the ferment being destroyed in the presence of acid.

It may seem strange that the hydrolysis of starch with the formula $C_6H_{10}O_5$ should result in the formation of dextrin with the same formula It must be remembered however that these formulæ are the simplest possible, and that the colloidal starch molecule is probably at least one hundred times as large as the molecule represented by $C_6H_{10}O_5$ The hydrolysis of the starch takes place by stages resulting in the production of a number of dextrins intermediate between starch and maltose The formation of maltose begins at the very onset of the hydrolysis, so that we may conceive the soluble starch molecule as made up of a number of groups $3(C_6H_{10}O_5)$ Each of these groups would take up one molecule of water with the formation of maltose and a dextrin

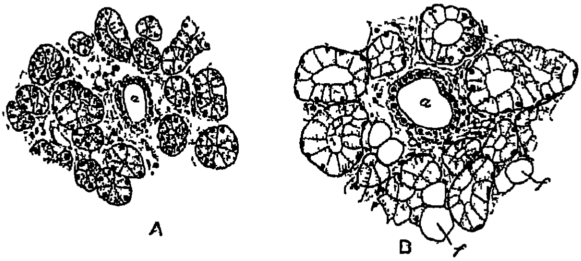
$$3(C_6H_{10}O_5) + H_2O = \underset{\text{Dextrin}}{C_6H_{10}O_5} + \underset{\text{Maltose}}{C_{12}H_{22}O_{11}}$$

The dextrins themselves however are in most cases more complex bodies than is here represented, belonging, like the parent molecule, to the class of bodies known as colloids.

THE MECHANISM OF SALIVARY SECRETION

The digestive juices are formed by the agency of glands. These are recesses or branching tubules lined with a continuation of the general alimentary epithelium. This secretory epithelium is separated by a basement membrane from the surrounding connective tissue, in which ramify blood-vessels, lymphatics, and nerves. The secretory cells are bathed by the lymph that exudes from the capillaries; and from this lymph they select the substances necessary for their nourishment, and form therefrom the special ingredients of their secretion, which they turn out into the lumen of the gland tubule. This process is an act of vital selection by the cell, and is not a mere filtration or transudation of certain constituents of lymph through the epithelial membrane.

FIG 161.



A, serous gland, B, pure mucous gland from mouth (Kölliker) *a*, ducts, *f*, fat cells

The salivary glands are divided into three classes, the mucous glands, the serous glands, and glands which partake of the characters of both these groups. Chief among the last class are the demilune glands, which are often spoken of as mucous.

Pure mucous glands are found scattered over the tongue and mucous membrane of the mouth (Fig. 161, B). They have large acini which are lined with large clear cells, distended with mucin. These acini open into a short duct lined with striated cubical epithelium. Their secretion is thick and viscid and consists chiefly of a solution of mucin. The serous glands occur as small follicles scattered over the lining of the oral cavity. They have small tubular acini which are lined with polyhedral granular cells (Fig. 161, A). Their secretion is watery and consists chiefly of water, salts, and ptyalin with a trace of albumen and globulin.

Of the three *large* salivary glands in man, the parotid, submaxillary, and lingual, the parotid represents a pure serous gland The other two belong to the class of demilune glands: in the submaxillary of man however, lobules of this nature are mixed with pure serous acini.

The demilune type conforms to the purely mucous gland in that its acini are large and are lined (in hardened specimens) by a complete layer of large clear swollen cells, which yield a mucous secretion. Between these cells and the basement membrane however is another type of cells which stain deeply with hæmatoxylin, are granular, and are denoted from their shape crescentic or demilune cells. These cells were formerly supposed to take the place of the mucous cells destroyed in the process of secretion, but they have their own system of ducts, and there seems little doubt that they are serous cells taking an active part in the secretory process.

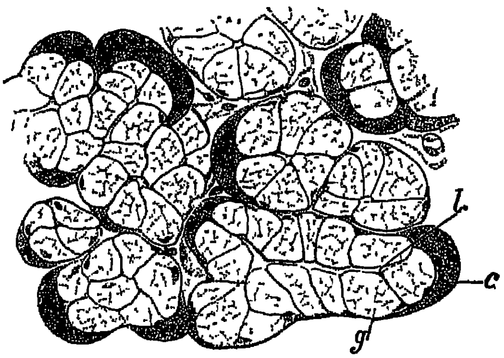
All these glands pour their secretions into the mouth, the active secretion being excited by the presence of food in the mouth, and by the movements of mastication.

Changes accompanying Activity

The salivary glands may be made to secrete by administration of pilocarpin or by stimulation of their nerves. On histological examination it is found that activity is associated with marked changes in appearance of the cells. If we examine a section of a mucous gland that has been in a resting condition for some time ('resting gland'), the acini are seen to be distended with large cells having clear hyaline contents, so close together that no lumen can be seen (Fig. 162). The nuclei situated at the outer border of the cells, near the basement membrane, appear shrivelled, with irregular margins.

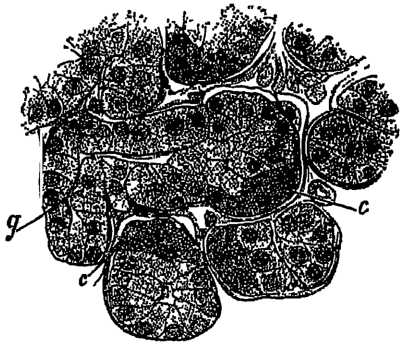
In a section made through a discharged gland (*i.e.* one that has been actively secreting for some time), the acini and the cells are smaller, the lumen quite distinct, and the nuclei round and swollen (Fig. 163). The whole section appears darker from the fact that the cells have taken up the staining fluid more readily. The difference between the sections depends chiefly on the fact that, in the sections of the resting gland, the cells are distended with mucin, which does not take up the staining agent and gives the cells their clear hyaline appearance. When secretion occurs, the mucin is discharged into the lumen, so that the cells shrink and consist more largely of protoplasm.

Fig. 162



Submaxillary gland of dog, after prolonged rest (Ranvier) *l*, lumen of alveolus, *g*, mucous cells, *c*, demilune cells

Fig. 163

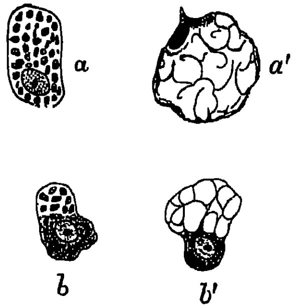


Same gland after prolonged activity.

If, instead of examining sections of hardened glands, we examine fresh glands teased in normal saline fluid, or fixed with osmic acid vapour, the appearance presented is quite different. The cells of the resting gland are not clear and hyaline, but are full of coarse granules. When secretion occurs these granules disappear. If to a fresh specimen of resting gland any of the ordinary hardening agents (such as spirit or Muller's fluid) be added, the granules are seen to swell up and fuse together to form a hyaline mass distending the cell. In fact the ordinary picture of the hardened resting gland is reproduced (Fig. 164).

We see then that the resting gland in a normal condition does not contain mucin, but contains a precursor of mucin—*mucigen*, which appears in the form of granules. As these are turned out of the cell they undergo some change, perhaps associated with imbibition of water, and are transformed into mucin.

Fig 164



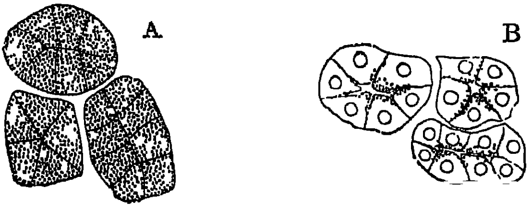
Mucous cells from a fresh submaxillary gland of a dog (Langley). *a*. Mucous cell examined fresh from a resting gland *a'* The same cell treated with weak alcohol *b* and *b'*. Cells from a discharged gland before and after treatment with weak alcohol.

Parotid

A similar change occurs in the serous glands when secretion takes place. The cells of the resting parotid gland, examined in normal saline fluid, are swollen and full of fine granules. With activity these granules are discharged, and the cells shrink and become clearer (Fig. 165).

In the pancreas of the rabbit, which is very similar in structure to a serous salivary gland, the changes coincident with secretion can be observed in the living animal, since here the gland is spread out between the layers of the mesentery, so that individual acini may be examined under high powers. When the resting gland is observed in this way, each acinus is seen to be composed of two zones, an outer clear zone and an inner granular zone. The outlines of the cells cannot be distinguished (Fig. 166). When secretion is excited by the injection of pilocarpin or other means, the inner zone clears up, the granules being discharged into the lumen; the homogeneous outer zone becomes wider, while the nuclei and borders of the individual cells can be clearly made out.

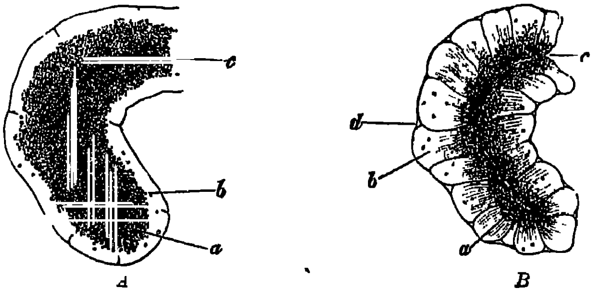
FIG 165.



Acini of a serous salivary gland A. Resting condition. B Discharged condition (Langley)

The amount of ferment to be extracted from the pancreas seems to be directly proportional to the number of granules present in the cells. But we have evidence, best marked perhaps in the case of the gastric glands, that these granules do not themselves represent the ferment but are merely precursors of the ferment, just as the mucigen granules in the submaxillary gland are precursors of mucin. These precursors of ferments are spoken of as *zymogens*.

FIG 166.



A terminal lobule of the pancreas of the rabbit *A*. In resting condition *B* After active secretion (Kuhne and Sheridan Lea)

Two changes occur in the cell when secretion takes place.

1. A transformation of zymogen granules into ferment, of mucigen into mucin, which substances are then discharged from the cell into the lumen of the gland.

2. A building up or reintegration of protoplasm, as evidenced by the growth in extent of the stainable protoplasmic parts of the cell.

During rest a twofold process is probably going on.

1. A further building up (anabolism) of the protoplasm of the cell out of the constituents of the surrounding lymph.

2. A katabolism or breaking-down of the cell-protoplasm, with the formation of zymogen granules, which are stored up in the cell till the economy requires that they should be converted into ferment and discharged into the lumen.

Active secretion is associated in the living body with—

1. Increased blood-supply. If secretion be excited in the submaxillary gland by stimulation of the chorda tympani nerve, a cannula having been previously inserted into the distal end of a vein coming from the gland, the amount of blood flowing from the vein is increased eight or ten times. Before excitation the blood drops slowly from the cannula; during excitation it runs freely, has a bright arterial red colour, and the stream may present pulsations, transmitted from the arteries through the capillaries.

2. Increased production of CO_2. The venous blood however appears bright red, since this increased production is more than compensated by the increased flow of blood through the gland.

3. Electrical changes.

If the outer surface and hilus of the submaxillary gland be led off to a galvanometer, it is found that there is a slight resting current passing in the dog's gland from hilus to outer surface When secretion is excited, this current undergoes modification in a positive or negative direction, and it seems that the two events of secretion—cell change and passage of fluid through the gland—may give rise to opposite results. Thus stimulation of the chorda tympani nerve gives a positive followed by a negative variation, stimulation of the sympathetic gives a pure negative effect The outgoing current therefore seems to be associated with the passage of fluid through the gland-cells.

It might be thought that the secretion was a result of the larger flow of blood through the gland, and indeed of the raised pressure in the capillaries, consequent upon the dilatation of the arterioles causing an increased transudation.

The following facts however show that secretion is an active process of the epithelial cells, and is not dependent on filtration.

1. If manometers be inserted in the carotid artery and in the duct of the submaxillary gland, the pressure of the secretion may be double as high as the blood-pressure in the carotid, so that fluid is flowing from the blood-vessels at a low pressure into the duct at a high pressure—a process not explicable by any theory of filtration.

2. If atropin be administered, stimulation of the chorda tympani nerve produces no secretion in the submaxillary gland, although dilatation of the blood-vessels takes place as usual.

3. Some secretion may be caused by stimulating the chorda tympani nerve in a head recently severed from the body.

4. If the submaxillary gland be enclosed in a plethysmograph, stimulation of the chorda tympani nerve causes a *shrinkage* of the gland, in spite of the concomitant vascular dilatation, showing that the fluid secreted is supplied immediately by the cells, and that these only recoup themselves later from the lymph and blood. A primary increased transudation from the blood-vessels would of course be accompanied by an increase in volume of the gland.

Nerve-supply

The salivary glands have a double nerve-supply, from the sympathetic and from the cranial nerves. The submaxillary gland receives its sympathetic fibres from branches of the cervical sympathetic which ramify on the facial artery, and its cranial fibres from the chorda tympani nerve. These fibres run for a short time with the lingual nerve, and then leave it as a slender nerve which, reaching Wharton's duct (duct of submaxillary gland), runs along this to the gland. The fibres are connected in the hilus of the gland with nerve-cells. A small collection of nerve-cells—the 'submaxillary' ganglion—is found in the triangle between the chorda tympani nerve, lingual nerve, and duct. With the cells of this ganglion are connected fibres of the chorda tympani going to supply the sublingual gland (Langley).

Different effects are obtained according as the chorda tympani or the sympathetic fibres are stimulated. Stimulation of the chorda tympani in the dog gives rise to an active dilatation of the vessels of the gland, and a copious watery secretion containing only a small amount of mucin and formed elements.

land
us watery
tion contain
formed

Stimulation of the sympathetic causes constriction of the vessels, and a scanty flow of very thick viscid saliva, rich in

Sympt.
striction of
ael.
ty flow of
viscid
iva rich in
e in
ges in cells
marked
ded that:-
fibres are
ators +
ion of H_2O
fibres are
strictor +
etor of Org.

Fig 167.

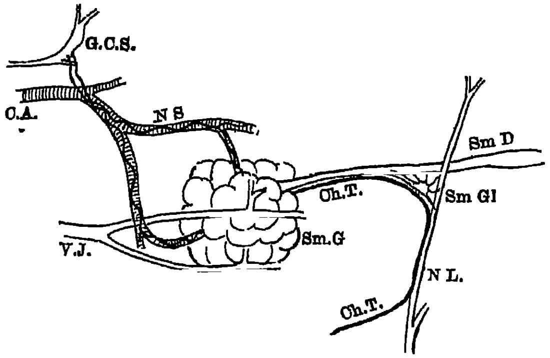


Diagram of nerve-supply to submaxillary gland Sm G Submaxillary gland N L Lingual nerve Ch T. Chorda tympani Sm Gl. Submaxillary ganglion Sm.D Wharton's duct V J Jugular vein C A Carotid artery. G.C S Superior cervical ganglion N.S Sympathetic fibres ramifying on facial artery (After Foster)

mucin and formed elements. The changes that occur in the cells are much more marked under sympathetic than under chorda stimulation. In consequence of the differences in the action of these two sets of nerve-fibres, they have been supposed to have two distinct functions. The chorda fibres are vaso-dilator and secreto-motor of water; the sympathetic fibres are vaso-constrictor and secreto-motor of organic matter. The latter have been also denoted trophic, because of the marked change in the cells that is caused by their stimulation. They might well be called the katabolic fibres of the gland.

fibres
trophic
marked
[illegible]
stimul
called
the fibres
Cons.

There is no doubt that the difference in the action of the two sets of nerves is in some degree dependent on the variations in the blood-supply produced at the same time, and that the chorda saliva is more watery because the gland-cells have more fluid at their disposal.

According to Langley the actions of the gland-fibres of the sympathetic and chorda tympani nerves are probably identical, the differences in the saliva obtained by stimulation of the two sets of nerves being conditioned by the concomitant vascular changes Against this view may be urged the fact that while atropin paralyses the secretory fibres of the chorda tympani, it has practically no effect on those derived from the sympathetic.

of Lang

The *parotid gland* has also a double nerve-supply: fibres from the cervical sympathetic, and cerebro-spinal fibres running in the auriculo-temporal branch of the fifth nerve, but originating probably from the glosso-pharyngeal and running through the tympanic branch of this nerve (nerve of Jacobson). Stimulation of the cerebro-spinal fibres produces in the rabbit and dog a copious flow of limpid saliva of low specific gravity. Stimulation of the sympathetic causes in the rabbit a scanty flow of saliva free from mucin, but containing more proteins and ferment than the cerebro-spinal secretion. In the dog stimulation of the sympathetic causes no secretion, although the changes, that we have already described as accompanying activity, take place in the cells.

Stiml
S/unnl
origena
fr Glos
geal:
thro' the
tympanl
in the
clear
tempo
of 5th
1. Cohe
Saliva
Stim P:

Reflex secretion.—The secretion of saliva is normally brought about reflexly by stimulation of the branches of the fifth and glosso-pharyngeal nerves distributed to the mucous membrane of the mouth and tongue, the stimulus being furnished by the presence of food in the mouth, by acids, or by the masticatory movements.

1. Scand
Saliv
mucin
more pr
ferm
2 In dog

The centre for the secretion of saliva is located in the medulla, since from this part of the central nervous system arise both the afferent and efferent nerves by which the secretion is regulated. The peripheral nerve-cells, such as the collection that goes by the name of the submaxillary ganglion, cannot act as reflex centres, and probably their sole function is to preside over the nutrition of the nerve-fibres distributed to the glands.

no Se
but the
later p
the ce

Paralytic secretion—If the chorda tympani nerve be cut on one side, the submaxillary gland enters into a condition of what we might term 'overflow activity' If a cannula be placed in Wharton's duct, a constant slight dribbling of saliva occurs (about 1 drop in 20 minutes). This is known as 'paralytic secretion.' Sections of the gland present the typical appearance of a resting gland This condition is attended by a gradual atrophy of the gland, which may lose half its weight in a few weeks Section of the sympathetic does not give rise to any analogous phenomenon, nor does it stop the paralytic secretion caused by section of the chorda

1. Gen
with ce
Clear
[illegible]
2 Not
[illegible]
3 Not
[illegible]
opera

ection of chorda on one side :-
. "over-flow activity", [illegible]
. Section of gland present appearance of a resting gland

Section of Sympath
[illegible]
2 [illegible]

SECTION 3

DIGESTION IN THE STOMACH

The food after thorough mastication and admixture with the saliva passes down the œsophagus into the stomach. Here salivary digestion continues until the reaction of the food is rendered acid by the secretion of gastric juice, a change which does not occur for twenty to thirty minutes or even longer. Thus the greater part of salivary digestion takes place in the stomach.

The stomach is a saccular dilatation of the alimentary canal, lying obliquely in the abdomen, with the œsophagus opening into its larger cardiac end or fundus, while its opposite right extremity gradually narrows to the pyloric orifice which opens into the duodenum. The wall is composed of four coats, the serous, muscular, submucous, and mucous coats. The mucous membrane in the contracted condition is thrown into folds, the submucous coat, which carries the large vessels and nerves, being very loose in texture. The mucous membrane consists of a delicate connective tissue rich in lymphoid elements, covered by a continuous layer of hyaline columnar cells, and presenting a number of minute pits which are the orifices of tubular glands set closely together so as to make up the greater mass of the mucous membrane. The gastric juice is formed by the activity of these glands.

[illegible] membrane
d in lymphoid
ments covered
hyaline [illegible]
columnar cells
presenting pits
are [illegible]
[illegible]
[illegible]
[illegible]
vessels
[illegible]

Two varieties of glands may be distinguished. At the cardiac end of the stomach the glands are simple tubules, with short necks or ducts. The secreting part of the tubule is lined with a single layer of small granular cubical cells (chief cells); between these and the basement membrane are a number of larger oval cells—parietal or oxyntic cells—which stain differently from the central cells.

In the pyloric region the glands consist of tubules which are branched at the end, and have a comparatively long neck or duct. In this region we find only chief cells, no oxyntic cells being present. The necks of all the glands are lined with columnar epithelium, similar to that covering the free surface of the mucous membrane.

The best method of obtaining pure gastric juice is that devised by Pawlow, in which the secretion is evoked by letting a dog eat meat after making openings in the œsophagus and stomach, so that the food eaten cannot enter the stomach. Or a diverticulum of the stomach may be established by making an incision as shown in Fig. 170, A, and then reflecting and suturing the mucous membrane, so that a little sac of the cardiac end is produced in nervous, vascular, and muscular continuity with the rest of the stomach, and separated from the latter only by a diaphragm consisting of a double layer of mucous membrane (Fig. 170, B). A secretion of

FIG 168

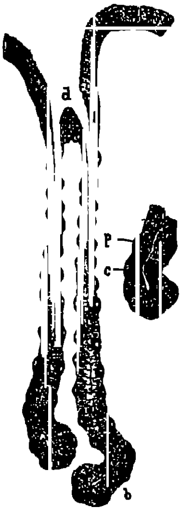


FIG. 169.

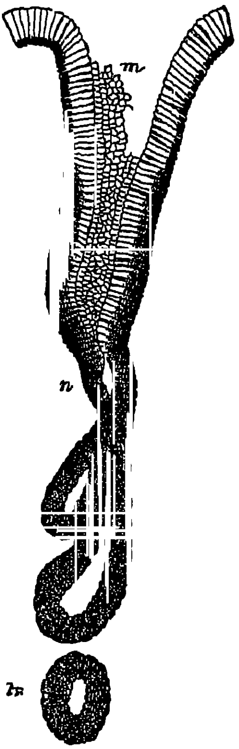


FIG. 168.—A gland from the cardiac end of the stomach (after Klein) *d*, duct of the gland, *b*, base of one of its tubules, *c*, central cell, *p*, parietal or oxyntic cell.
FIG 169—A pyloric gland (Ebstein). *m*, mouth, *n*, neck, *tr*, deep portion of one of the tubules cut transversely

gastric juice may then be evoked at any time by allowing the animal to eat in the ordinary way. Thus obtained it is a clear, colourless, acid liquid, with a specific gravity varying from 1001 to 1010. Its chief constituents are two ferments, pepsin and rennet ferment; and free hydrochloric acid. The amount of free HCl in the gastric juice varies from 0·2–0·3 per cent. in man to 0·6 per cent. in the dog and cat. It also contains salts, and a large amount of water which constitutes about 98 per cent. of its bulk.

The hydrochloric acid is shown to exist in a free condition from the fact that on elementary analysis the amount of chlorine present is more than sufficient to saturate the bases.

FIG 170.

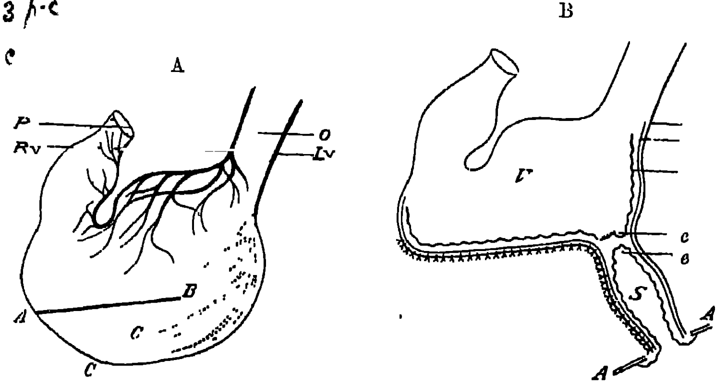


Diagram to show Pawlow's method of making a cul-de-sac of the cardiac end of the stomach, with vascular and nerve supply intact. In A the line of the incision into the stomach wall is shown. B represents the operation as completed In A *O*, œsophagus, *R v.*, *L v*, right and left vagus nerves, *P*, pylorus, *C*, cardiac portion of stomach, *A*, *B*, line of incision In B *V*, main portion of stomach, *S*, cardiac cul-de-sac, *A*, abdominal wall, *e*, *c*, mucous membrane reflected to form diaphragm between the two cavities

It is often of importance to be able to determine the presence of free mineral acid (HCl) in the gastric contents Mere acidity to litmus may be due to lactic or fatty acids produced by fermentation of the contents The following reactions may be used to test this point

a Paper stained with congo-red turns blue in the presence of free inorganic or organic acids, but is not altered by acid salts

b. To some of the stomach-contents an equal quantity of Gunzberg's reagent (a solution of phloroglucin and vanillin in alcohol) is added and the mixture evaporated on a water-bath. A delicate rose tint shows the presence of hydrochloric acid *c* A drop of saturated solution of tropæolin OO is allowed to evaporate on a porcelain slab at 40° C., and while at this temperature a drop of the liquid to be tested is added. On evaporation a violet stain is left if free HCl be present.

An artificial gastric juice may be prepared by digesting the fresh mucous membrane of the stomach with 0·2 per cent. HCl at 40° C. for some hours and then filtering from the undissolved nucleins of the cells. The fluid thus obtained contains a large proportion of albumoses mixed with the pepsin. In order to get this latter approximately pure, the digestion is continued for three weeks, by which time the greater proportion of the proteins are converted into peptones. On saturating the fluid with ammonium sulphate, the whole of the pepsin is thrown down contaminated only with a slight trace of unconverted albumoses. This precipitate mixed with 0·4 per cent. HCl gives a powerful artificial gastric juice. The simplest method is however to extract the fresh mucous membrane with glycerin. A few drops of the glycerin extract added to dilute HCl makes an effective digestive mixture.

ACTION OF GASTRIC JUICE ON THE FOOD

The chief action of gastric juice is on proteins, which it converts into albumoses and peptones. This action is easily studied if we take some washed fibrin and put it in 0·2 per cent. hydrochloric acid. In this acid the fibrin swells up and becomes transparent, but does not dissolve, even though kept at 40° C. for some time. If now to the swollen-up mass we add some gastric juice, or a few drops of glycerin-extract of gastric mucous membrane, the fibrin is speedily dissolved and a clear solution results. Neutralisation of the fluid with alkali throws down nearly the whole of the protein present as acid albumen. If however the action be long continued, the neutralisation precipitate becomes less and less, and the fluid contains chiefly albumoses with a little peptone. These may be shown to be present by the following tests.

Nitric acid gives a precipitate which dissolves on heating and reappears on cooling.

Caustic potash and a trace of copper sulphate give a pink colour, which turns to violet on the addition of more copper sulphate—biuret reaction.

Saturation with ammonium sulphate gives a copious precipitate of albumoses. If this be filtered off, the filtrate contains a small amount of peptone. To produce any large quantity of peptone the gastric juice must act for a considerable length of time.

The stages in the action of gastric juice on proteins are therefore—

Coagulable protein.
Syntonin or acid albumen.
Albumoses.
Peptones.

The action of gastric juice on proteins resembles that of ptyalin on starch in that it consists of a series of hydrolytic changes, converting the large indiffusible coagulable or coagulated molecule into a number of smaller non-coagulable more soluble and more diffusible molecules. The study of the disintegration products of proteins (p. 33) has shown however that they are much more complex in constitution than the starches, and hence we find a greater variety among the first products of their hydrolysis. The number of albumoses and peptones is probably large, but we are able to group them into fairly definite classes according to the stage in digestion at which they are produced. In the process of digestion the proteins undergo progressive disintegration, so that the first products, the primary albumoses, are large molecules reacting to saline precipitants like globulins, while the latest stages, the peptones, are small molecules, not precipitated by neutral salts, and, relatively to proteins, diffusible. The stages in the peptic digestion of fibrin are shown in the following table:

Fibrin.
|
Soluble globulin, coagulating at 56° C.
|
Acid albumen.
|
Primary albumoses (proto- and hetero-albumose).
|
Secondary albumoses (deutero-albumoses).
|
Peptones.

Kühne's method for the separation of these bodies from a gastric digest of fibrin can be carried out in the following way.

Neutralise—Acid albumen precipitated.
Boil in slightly acid reaction—Coagulable proteins precipitated
The filtrate contains only albumoses and peptones.

Saturate filtrate with solid NaCl, all the hetero-albumose and the greater part of the proto albumose are precipitated This precipitate is collected, dissolved in water, and dialysed. As the salt passes out the hetero-albumose is precipitated, being insoluble in pure water, while the proto-albumose remains in solution and can be precipitated by concentration and addition of absolute alcohol

The filtrate from the primary albumoses is treated with a little glacial acetic acid previously saturated with NaCl. This throws down the last traces of proto-albumose and a little deutero-albumose The precipitate is filtered off, and the filtrate saturated at boiling temperature with ammonium sulphate, which precipitates all the deutero-albumoses This precipitate is filtered off and concentrated to separate off the greater portion of the Am_2SO_4. The last traces of Am_2SO_4 are got rid of by the addition of baryta, and after filtering off the $BaSO_4$ precipitate, and boiling off the ammonia, the peptones are precipitated by adding a large excess of absolute alcohol, or by means of phosphomolybdic acid

By means of fractional precipitation with ammonium sulphate, Pick has separated three deutero-albumoses, which are designated as A, B, and C deutero-albumose These can be further subdivided by treatment with alcohol, which dissolves certain of the albumoses and leaves others Among the products so separated may be mentioned a thio-albumose, rich in sulphur, and a glyco-albumose, containing the greater part of the carbohydrate moiety of the original protein These various bodies also differ according to the nature of the monamino-acids and the amount of basic nitrogen they yield on hydrolysis The peptone obtained by Kühne's method may also be divided into a peptone insoluble in alcohol which contains carbohydrate, and a peptone soluble in alcohol which yields no carbohydrate radicle on hydrolysis, and therefore does not give the Molisch reaction.

The later stages of gastric digestion are by no means rapid, so that even after twenty-four hours' digestion the greater portion of the proteins are found in the form of albumoses.

Gastric juice acts in the same way on insoluble coagulated proteins, dissolving these and converting them into acid albumen, albumoses, and peptone.

Gelatin is converted by gastric juice into bodies known as gelatin peptones, and in this conversion loses the power of forming a jelly when cold.

Collagen, the constituent of the connective tissues from which gelatin is obtained on prolonged boiling, is also digested by gastric juice, giving rise to the same end-products as gelatin.

In this way the connective tissue binding together the fat-cells of adipose tissue is broken up and dissolved, and the fat is set free in a liquid form, ready to be acted on by the pancreatic juice.

Another important function of the gastric juice depends on the fact that dilute hydrochloric acid acts as an antiseptic. Meat and fibrin may be kept for several days in gastric juice without undergoing decomposition. If however the acid be neutralised, decomposition sets in rapidly on exposure to air, and at the end of twenty-four hours the mixture has a fœtid odour, and is found to be swarming with bacteria. This action is of great importance in the normal life of the individual. The microbes which have been shown to be the causes of typhoid and cholera are destroyed by gastric juice. Hence there is little likelihood of contracting these diseases unless the secretion of gastric juice be insufficient, or the acid neutralised by the presence of alkalies or rendered inert by too much dilution.

On starches and fats gastric juice has no action Ingestion of large amounts of cane-sugar gives rise to a free secretion of mucus on the surface of the gastric mucous membrane, and this mucus is said to contain an invert ferment which has the power of converting cane-sugar into dextrose and lævulose. A certain amount of inversion must also be caused by the action of the dilute HCl at the body temperature. The same factor would convert some of the maltose formed by the salivary digestion into dextrose.

Circumstances affecting activity of gastric juice.—Gastric juice is most active at about 40° C. At 0° its action is indefinitely suspended. If boiled the ferment is destroyed. The action goes on most rapidly when the proportion of HCl present is 0·4 per cent.; larger amounts of acids hinder its action. Neutralisation stops the action altogether, and if the juice be rendered slightly alkaline and be kept at the temperature of the body for a short time, its activity is permanently destroyed. Its action is also hindered if the products of its activity be allowed to accumulate to a large extent. In the stomach this is guarded against by the continual absorption through the gastric mucous membrane of the albumoses and peptones as they are formed.

Action of Gastric Juice on Milk

Milk, which is the sole diet of the infant, is in itself a whole food, and contains representatives of all five classes of foodstuffs—proteins, fats, carbohydrates, salts, and water. The chief protein of milk—caseinogen—is a body allied to the nucleo-albumens. From the gastric mucous membrane, especially in young animals, a ferment may be extracted known as rennet ferment or *rennin*. On adding a few drops of rennet solution to milk, and warming the mixture to about 40° C., it sets into a solid mass, so that the vessel may be inverted without spilling the contents. On allowing the clot or curd to stand it shrinks, enclosing in its meshes the greater part of the fat-globules of milk, so that the clot floats in an almost transparent fluid (whey). This clotting depends on a change induced in the caseinogen of the milk under the action of the ferment.

Pure caseinogen may be prepared in the following way. A litre of ‘separated’ milk (*i.e.* milk that has been freed from cream by the use of a centrifuge) is diluted with 9 litres of distilled water in a tall glass vessel and 10 c.c. of glacial acetic acid added and the mixture stirred. A flocculent precipitate of caseinogen is produced, and rapidly sinks to the bottom of the vessel. The precipitate is collected, pressed between linen, and rubbed up in a mortar with 20 c.c. of ammonia, and water added to 5 litres. The solution is allowed to stand for some hours, any fat which may rise to the top being skimmed off. Acetic acid is added as before, and the resultant precipitate is washed several times by decantation with distilled water, and finally collected on a filter and pressed free of fluid. This precipitate may be dissolved in weak soda or potash, forming a clear solution. If it be dissolved in lime-water an opalescent solution is formed. If rennet be added and the mixture allowed to stand at 40° C., a clear colourless clot of casein is produced. This act of clotting, just as the clotting of blood, is intimately dependent on the presence of a neutral salt of lime. If the precipitate of caseinogen be washed till all lime salts are removed, addition of rennet causes no clotting; but the mixture of caseinogen and rennet clots at once on addition of calcium phosphate or chloride.

Thus in clotting of milk two processes are concerned:

1. A conversion of caseinogen into some other body which may be called soluble casein.

2. A combination of this soluble casein with a lime salt to form insoluble casein, which is precipitated in a gelatinous form.

These facts are well shown by the following experiment of Ringer. Two test-tubes are taken, *a* and *b*, containing a solution of pure caseinogen free from lime. To *a* rennet ferment is added, and to *b* a solution of calcium chloride; and the two tubes are kept at 40° C. for some time. No visible reaction takes place. If *a* be now boiled, so as to destroy the rennet ferment present, and on cooling a few drops of calcium chloride be added, clotting occurs. In this experiment the rennet ferment has evidently produced some change in the caseinogen although no clotting took place, since the boiled fluid needs only the addition of lime salt to make it clot. The fact that *b* did not clot shows that lime salts are without effect on a solution of caseinogen which has not been previously exposed to the action of rennet ferment.[1]

THE SECRETION OF GASTRIC JUICE

The functions of the two different kinds of gastric glands have been determined by cutting out a portion of the cardiac or pyloric parts of the stomach, and sewing its edges to the margins of the abdominal wound. The gap in the gastric wall thus produced is closed by suturing the edges together, so that the final result of the operation is that the stomach is rather smaller, and there is a little cul-de-sac consisting of either cardiac or pyloric mucous membrane communicating with the exterior. Secretion may be excited by mechanical irritation of this mucous membrane by the introduction of a sponge or some food, and the juice may be collected. It is better however to make the cul-de-sac as described on p. 317, leaving the nervous connections of the mucous membrane intact. Under these conditions the isolated portion of the stomach secretes whenever food is taken by the mouth into the main stomach, and the secretion may be regarded as practically normal in all respects. It is then found that a cardiac cul-de-sac contains free HCl and pepsin, and so has the power of digesting proteins. A pyloric cul-de-sac, on the other hand, yields a secretion which is neutral or slightly alkaline, but which is shown to contain pepsin from the fact that, on adding 0·2 per cent. of hydrochloric acid, the juice is able to digest proteins. This shows that both cardiac and pyloric glands yield pepsin, but only the cardiac glands yield free hydrochloric acid. Since in both sets of glands the central cells are the same, it is concluded that these cells give rise to the pepsin, while the large oval parietal cells in the cardiac end form the free hydrochloric acid. [illegible]

---

[1] The student must be careful to distinguish between the curdling of milk by rennet and its curdling by addition of acid, or when it becomes sour in consequence of the development in it of lactic acid. In the former case the curdling is a true clotting, and is due to the conversion of the soluble caseinogen into the insoluble casein, in the same way as when fibrinogen is converted into fibrin. When acid is added to milk the caseinogen is merely precipitated, just as uric acid is precipitated by addition of HCl to a solution of a urate. And this precipitate can be dissolved up again as caseinogen and made to clot, *i.e.*, can be converted into casein by the agency of rennet ferment.

Coincident with activity, changes take place in the central cells analogous to those which we studied in the case of the salivary glands. The central cells of the glands from a fasting stomach (*i.e.* of an animal that has not taken food for eighteen hours) are swollen and filled with granules. When secretion occurs two zones can be distinguished, an outer protoplasmic zone, free from granules, and an inner granular zone, which becomes less and less marked as secretion proceeds. These granules consist of a zymogen, *pepsinogen*. If the fresh mucous membrane be extracted with glycerin, much less ferment is obtained than if the extraction be performed after treatment of the mucous membrane with dilute acid. The pepsinogen is further distinguished from the pepsin by the fact that it is only slowly affected by a solution of sodium carbonate, which very rapidly destroys pepsin. Thus if an acid extract of the gastric mucous membrane be made alkaline to the extent of 1 per cent. sodium carbonate, the whole of the pepsin is destroyed within thirty seconds. On the other hand a neutral watery extract of the membrane may be made alkaline for two or three minutes, and on then adding HCl to 0·2 per cent. it is found that the mixture has a strong digestive action. The acid extract contains pepsin which is destroyed by the carbonate. The watery extract contains chiefly pepsinogen and is therefore only slowly altered by the treatment.

The secretion of gastric juice may be excited by direct stimulation of the mucous membrane by the presence of food, etc., in the stomach. We have evidence that a copious flow of gastric juice may be excited through nervous channels, either reflexly through the mouth or in consequence of events occurring in the brain. This reflex secretion is well shown in the following experiment:—The œsophagus of a dog is divided in the neck, and the two ends stitched to the wound so that they open exteriorly. At the same time a gastric fistula is made. The dog is fed and kept in good condition by the introduction of milk into the lower end of the œsophagus, or by the direct introduction of food into the stomach. When the animal has quite recovered, he is starved for nine hours and is then allowed to eat meat. The dog eats greedily, and, since the food cannot reach the stomach but tumbles out by the opening of the œsophagus in the neck, will go on eating for a very long time. Directly the dog begins to eat, a copious secretion of gastric juice is obtained, as much as 300 c.c. of pure gastric juice being poured out in one hour, clear and colourless like water. The same effect may be produced by simply showing the dog a piece of meat, and it is stated that the flow ceases as soon as the dog realises that he is not intended to have the meat. Pawlow, to whom we owe the above experiment, has shown that the efferent nerve in the reflex, that is to say, the secretory nerve to the stomach, is the vagus. If proper precautions be observed, stimulation of the vagus causes invariably a secretion of gastric juice.

In testing the action of the vagus on the gastric secretion, we have to bear in mind that the activity of the gastric glands is reflexly inhibited by all painful stimuli, and is abolished by any stoppage of the blood-flow or by the action of anæsthetics. The experiment is therefore carried out in the following way:—On one day the gastric fistula is established, and one vagus in the neck divided and ligatured, the ligature being allowed to hang out of the wound. Four days later the animal is placed in an upright position, the vagus drawn out of the wound and stimulated with induction-shocks at the rate of one or two a second. The animal is not anæsthetised and the experiment is unattended with pain. The cardio-inhibitory fibres are degenerated in consequence of the section, so that the stimulation does not alter the blood-pressure in any way. After a latent period of four or five minutes, gastric juice begins to drop from the cannula in the fistula, and the secretion can be obtained as often as the nerve is stimulated. Section of both vagi stops the reflex secretion of gastric juice normally evoked by the sham feeling described above

There are however two sets of factors involved in the normal secretion of gastric juice. The more important is the nervous mechanism described above, set into action from the mouth or the cerebral cortex under the influence of appetite, and having as its efferent channel the vagus nerve. This mechanism is destroyed by section of both vagi. It is then observed that introduction of food into the stomach evokes a secretion of juice, which comes on one to two hours later, and lasts a considerable time. If a diverticulum of the stomach has been made, introduction of food into the main stomach excites in this way secretion in the isolated cul-de-sac. Edkins has recently shown that the mechanism of this latter secretion is chemical. Under the influence of the food, some substance, a chemical messenger or ‘hormone,’ is produced in the pyloric mucous membrane, is absorbed into the blood, and carried to all parts of the mucous membrane, in which it acts as a specific excitant of the gastric glands, evoking a secretion of gastric juice

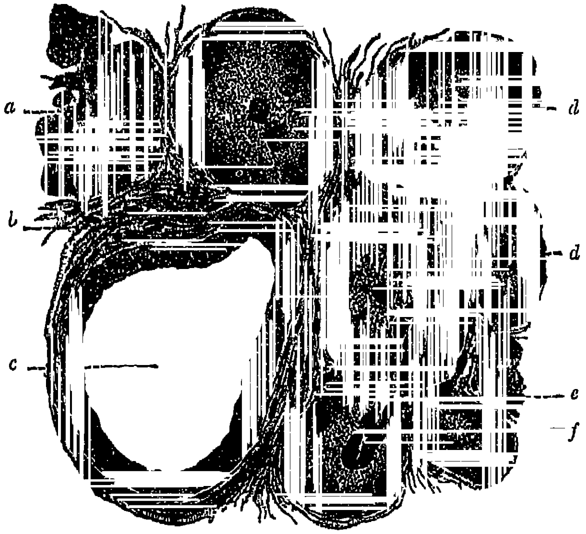
SECTION 4

PANCREATIC JUICE

The food, after being acted on by the gastric juice, is gradually passed on as the fluid chyme into the duodenum, the first part of the small intestine. Here it is subjected to the action of three secretions, the pancreatic juice, the bile, and the succus entericus.

The pancreas lies in the curve formed by the duodenum, and pours its secretions into that viscus by a duct which joins the duct from the liver and opens at a point about two or three inches below the pylorus. It is a tubulo-racemose gland, somewhat similar to a salivary gland. Its tubules however are much longer than those of the parotid. The tubules are lined with polyhedral cells, the inner two-thirds of which are granular, while the outer third is free from granules and stains darkly with hæmatoxylin. Activity is associated with a discharge of these zymogen granules, so that the cells

FIG. 171



Section of human pancreas (Böhm and v. Davidoff) × 450 *a*, cell-nest between acini, *b*, connective tissue, *c*, large duct, *d*, *d*, alveoli, *e*, duct passing into alveoli, *f*, inner granular zone of acinus shrink and become clearer. At the same time there is a growth in the protoplasm, so that in a discharged gland nearly the whole of the cell stains with hæmatoxylin.

On examining a stained section of pancreas under the microscope, we rarely fail to see here and there small circumscribed patches of epithelioid cells which have very little affinity for dyestuffs, and therefore appear as lighter areas in the section (*a*, fig 171) The cells are often arranged in short columns or clusters, and but little trace of an alveolar structure can be made out These structures, which are known as the 'islets of Langerhans,' have often been regarded as a special tissue planted in the midst of the ordinary secreting tissue of the pancreas It has been shown by Dale however that the number of these islets is markedly increased by activity, and that, in a gland which has been thoroughly exhausted, the larger part of the secreting substance loses its staining properties and becomes converted into islet tissue. One must therefore regard these islets as a phase in the life history of the secreting cells, and as representing an extreme stage of exhaustion of these cells. Whether they recover their staining properties and resume their secretory activity, or whether they are removed altogether to make room for newly formed glandular tissue, is not yet thoroughly made out, though the fact that at a certain period of fœtal life all the pancreatic cells have the appearance of islet cells is certainly in favour of the former alternative.

In order to collect pancreatic juice for examination and to investigate the conditions of its formation, it is necessary to make a pancreatic fistula. To make a permanent fistula, the abdomen (of a dog) is opened in the middle line, the first part of the duodenum drawn up to the surface, and a lozenge-shaped piece of the duodenal wall cut out, in such a position as to include the orifice of the chief pancreatic duct. The margins of the wound in the gut are then stitched together so as to restore its continuity, and the little piece of excised duodenal wall is stitched into the opening in the abdominal wall. When the wound is healed, the nipple-like orifice of the duct is seen on the surface of the abdomen in the middle of a small red patch of mucous membrane. To make a temporary fistula, it is only necessary to expose the duct at its entry into the duodenum and insert into it a small cannula, connected with a rubber tube through which the juice is allowed to flow into a suitable vessel.

In an animal with a permanent fistula no flow of juice occurs so long as it is in a fasting condition. At a variable period after a meal has been taken, a flow of juice begins and continues for several hours. It can be shown that the flow of juice follows immediately the entrance of the acid chyme into the duodenum, no flow being excited so long as the food remains in the stomach. The flow of juice can in fact be evoked at any time by the introduction of weak acid (*e.g.* 0·4 per cent. HCl) into the duodenum or the upper part of the small intestine. No effect follows the introduction of acid into the lower part of the ileum or into the large intestine. The effective stimulus to pancreatic activity is therefore the presence of acid in the upper part of the small intestine. duodenum

q How is this stimulus conveyed to the pancreatic cells? It was thought by Pawlow and other physiologists that the medium of transmission here, as in the case of the salivary glands, was the nervous system—either the central nervous system by means of the vagi, or peripheral collections of ganglion cells round the abdominal vessels and in the pancreas itself through the fine nervous filaments which pass between these and the intestinal wall. This idea however had to be abandoned when it was found that introduction of acid into a loop of small intestine, entirely freed from nervous connection with the rest of the body, produced a flow of pancreatic juice as profuse as that obtained from a loop of normal intestine. In the former case the only connection of the intestine with the pancreas was by means of the blood.

We must therefore conclude that the stimulus is a chemical one, produced in the mucous membrane by the action of the acid and carried thence to the pancreas in the blood stream. If the mucous membrane be scraped, and the scrapings rubbed up with dilute hydrochloric acid, and the mixture be then boiled, neutralised, and filtered to separate the proteins, a clear colourless filtrate is obtained, which, on injection in small quantities into the blood stream, evokes a copious flow of pancreatic juice. A watery or normal saline extract of mucous membrane has no effect. These facts prove that the mucous membrane of the upper part of the small intestine contains a body, which may be called *prosecretin*. Under the influence of dilute acids this body is converted into or gives off another substance, *secretin*, which is a specific stimulus for the pancreatic cells. This secretin is discharged by the cells, not into the intestine, but into the blood stream. By the blood it is carried to all parts of the body, and on passage through the pancreas, excites secretion of pancreatic juice.

Secretin is apparently a body of relatively simple constitution. It is soluble in acid, neutral, or alkaline solutions, or in alcohol. It is diffusible, and is not destroyed by boiling. It is not a ferment. It has not yet been isolated.

CHARACTERS AND ACTIONS OF THE PANCREATIC JUICE.

The juice obtained from a permanent fistula after a meal, or from a temporary fistula as the result of introduction of acid into the duodenum or the injection of a solution of secretin into the blood stream, is a clear colourless liquid, strongly alkaline from the presence of sodium carbonate. It contains from 1·5 to 3·5 per cent. total solids, of which about 0·5 to 2·5 are coagulable proteins. It has a digestive action on all three classes of foodstuffs. It converts starches into dextrin and sugar by means of a ferment, amylopsin; it hydrolyses fats by means of its ferment, steapsin; and after entry into the gut it contains a strong proteolytic ferment, trypsin. If however the juice be collected by a cannula in the duct, so as to prevent any contamination by the intestinal mucous membrane, it has only slight proteolytic powers, taking twelve hours to dissolve fresh fibrin, and being without action on coagulated egg albumen or gelatin. The addition of a few drops of succus entericus or a fragment of intestinal mucous membrane into the fresh juice, rapidly converts it into one of the most powerful proteolytic agents with which we are acquainted.

Protein
Carboh
the 3 cla

The proteolytic ferment contained in the juice under these circumstances is known as trypsin. The juice as secreted contains a precursor of this ferment, known as trypsinogen, which, under the action of a ferment, *enterokinase*, secreted by the intestinal mucous membrane, is converted into trypsin.

Glycerin extracts of a fresh pancreas have a marked amylolytic action, but have practically no proteolytic action unless the extract has been contaminated with intestinal contents containing enterokinase, the smallest trace of which will in time convert almost any quantity of trypsinogen into trypsin. The action of pancreatic extracts on fats is only observed in perfectly fresh extracts, the steapsin apparently undergoing rapid spontaneous destruction.

Action on Proteins

Proteins are converted by trypsin into albumoses and peptones, as in the case of the gastric juice. Trypsin however is only active in an alkaline or neutral medium, and is inert in the presence of an acid. If fresh fibrin be digested with this juice, it does not swell up but is gradually eroded and dissolved at the edges. The first product of its action is not acid- but alkali-albumen. Another important difference of this ferment from pepsin lies in the fact that it carries on the process of decomposition still further, causing a profound disintegration of the protein molecule, resembling that brought about by the action of boiling hydrochloric acid. The final results therefore of tryptic digestion are a number of bodies of comparatively small molecular weight, belonging to the series of bodies described as amino-acids and hexone bases.

In consequence of the much greater activity of trypsin as compared with pepsin, the first stages of proteolysis are much more rapid with the first-named. At no period of the process is it possible to detect the presence of primary albumoses, the alkali-albumen being directly converted into deutero-albumoses and peptones.

The end-products of pancreatic digestion include nearly the whole series of monamino- and diamino-acids which can be obtained by the action of acids on proteins.

These may be enumerated as follows :—

A. Mono-amino-acids.
- I. Monobasic acids of fatty series.
  - Glycine (amino-acetic acid). ✓
  - Alanine (amino-propionic acid).
  - Serine or oxyalanine (oxyamino-propionic acid).
  - Amino-valerianic acid. ✓
  - Leucine (amino-isobutyl-acetic acid)
  - Isoleucine (amino-caproic acid). ✓
- II. Dibasic acids.
  - Aspartic acid (amino-succinic acid).
  - Glutamic acid.
- III. Benzene derivatives.
  - Phenylalanine.
  - ✓ Tyrosine (oxyphenyl-alanine).

B. Heterocyclic compounds (*i.e.* ring compounds like benzene, but containing both C and N in the closed ring.

Proline[1] (pyrrolidine carboxylic acid).
Oxyproline (oxypyrrolidine carboxylic acid).
Tryptophane (indolamino-propionic acid).

C. Diamino-acids and allied bodies, strongly basic in character (the 'hexone bases').

Lysine (diamino-caproic acid).
Arginine (guanidine amino-valerianic acid).
Histidine (imidazol amino-propionic acid).
Diamino-trioxydodecoic acid (derived from a 12-carbon acid).

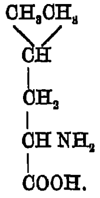
D. Sulphur-containing body.

Cystine (derived from amino-thio-lactic acid).
Methionine

Not all of these are to be obtained from every protein. All proteins however yield a large number of different amino-acids.

Two of these substances, namely, leucine and tyrosine, have long been known, owing to the ease with which they may be separated from a pancreatic digest.

Leucine belongs to the fatty series, being amino-isobutyl-acetic acid—



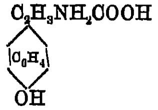
$$\begin{array}{c} CH_3\;CH_3 \\ \diagdown\;\diagup \\ CH \\ | \\ CH_2 \\ | \\ CH\,NH_2 \\ | \\ COOH. \end{array}$$

When pure it crystallises in white transparent plates, but in the impure state, as it separates out on concentrating a pancreatic digest, it forms microscopic globules with radial or concentric striation, often spoken of as 'leucine cones' (Fig. 172). About 10 to 20 per cent. of leucine may be obtained from most proteins.

---

[1] Phenylalanine and proline are not found free in a pancreatic digest, being combined to form a polypeptide

Tyrosine is an amino-fatty acid in combination with an aromatic group. Its constitution is shown by its formula, its



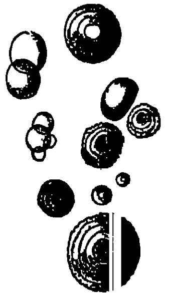
$$C_2H_3NH_2COOH \quad C_6H_4 \quad OH$$

full name being

$$\underbrace{\text{para-oxyphenyl}}_{\text{aromatic moiety}}\text{-}\alpha\text{-}\underbrace{\text{amino-propionic acid}}_{\text{amino-fatty acid}}.$$

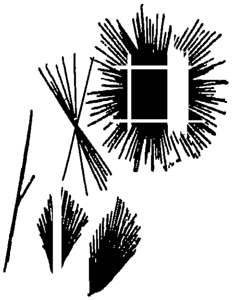
It crystallises in long slender needles aggregated into sheaves and rosettes (Fig. 173). It is very sparingly soluble in water and alcohol, and so is easily separated from pancreatic digests, often crystallising out spontaneously at the bottom of the liquid. It forms only 2-3 per cent. of the original protein.

Fig 172.



Leucine 'cones' (imperfect crystals) (Frey)

Fig 173



Tyrosine crystals (Frey)

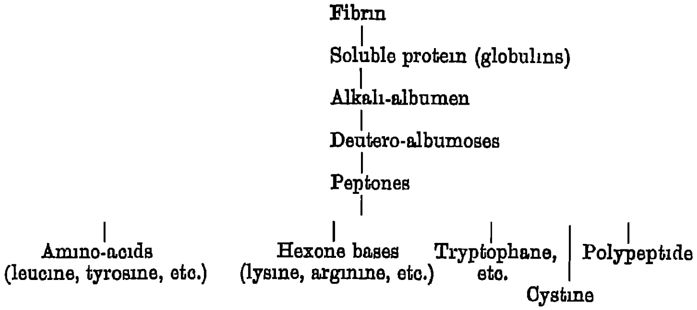
Aspartic acid (amino-succinic acid $C_2H_3(NH_2)(COOH)_2$) is also formed in small quantity in the pancreatic digestion of proteins. It forms, however, the greater part (35 per cent) of the amino-acids obtained by digestion of the proteins of wheat.

Antipeptone is a name which has been given to the precipitate obtained by treating the digest with phosphomolybdic acid, after separation of the chief amino-acids. Although it gives the biuret test, it does not give any coloration with Millon's reagent, and is not properly included in the class of peptones. It is probably a mixture of bodies, including the bases, lysine and arginine, the former being diamino-caproic acid $C_5H_9(NH_2)_2COOH$, and the latter a body analogous to creatine and giving rise, like creatine, to urea on heating with baryta water. In addition to these bases a small amount of ammonia is set free during the proteolysis.

A certain proportion of the nitrogen is in the form of a polypeptide which on further hydrolysis yields several amino-acids of the fatty series as well as the greater part of the phenyl-alanine and proline contained in the original protein

Another constant product of the pancreatic digestion of proteins is *tryptophane*, a body belonging to the aromatic group, and giving a typical red colour with bromine. To the presence of this group in proteins is due the reaction of Adamkiewicz and Hopkins, viz a purple colour on treatment with strong sulphuric acid and glyoxylic acid, or glacial acetic acid contaminated with the latter substance.

The changes involved in the pancreatic digestion of proteins may therefore be represented as follows:


Fibrin
Soluble protein (globulins)
Alkali-albumen
Deutero-albumoses
Peptones
Amino-acids (leucine, tyrosine, etc.)
Hexone bases (lysine, arginine, etc.)
Tryptophane, etc.
Polypeptide
Cystine

In the case of coagulated protein, there is apparently no formation of soluble proteins or alkali-albumen, the first product of proteolysis which can be separated being deutero-albumose.

Until recently, it was thought that the small molecules, which constitute the end products of pancreatic digestion, must be practically valueless for the purposes of nutrition, and that the main use of the energetic action of the trypsin was the gain of time in the first stages of proteolysis. It must be remembered however that we employ as food numbers of different kinds of proteins, whose constitution diverges considerably from that of the proteins building up our tissues. A man can make muscle protein out of the most various kinds of vegetable protein, whether from peas, beans, or wheat. For this conversion to take place the protein molecule must be first resolved into its constituent parts, out of which a new and different protein can be built up. A thorough disintegration is therefore a necessary preliminary to the assimilation of any foreign form of protein, and it is this thorough disintegration that is effected by the pancreatic juice, working with the succus entericus. Loewi has succeeded in keeping dogs in health, and in a state of nitrogenous equilibrium, for some time on a diet consisting, so far as its nitrogen was concerned, entirely of the ultimate products of pancreatic digestion.

Since the bacteria of putrefaction thrive readily in a slightly alkaline solution of protein such as pancreatic juice, care must be taken in all experiments with this juice to prevent putrefaction. To this end thymol or 1 per cent. sodium fluoride may be mixed with the solution. If this precaution be omitted, the mixture at the end of twenty-four hours has a foul odour, and is found to be swarming with bacteria, under the agency of which the proteins are further split up, with the formation of many amino-acids, free fatty acids, and aromatic bodies such as phenol, indol, and skatol. To the presence of the last two bodies is due the horrible fæcal odour of a pancreatic digestion-mixture which has been allowed to stand without the addition of an antiseptic. These aromatic substances are produced from the tryptophane (indoxyl aminopropionic acid), which is one of the *primary* decomposition products of proteins.

Gelatin is affected by pancreatic juice in the same way as by gastric juice, being converted into gelatin-peptones, which do not gelatinise on cooling. This juice however is unable to dissolve collagen, the chief constituent of the connective tissues. Hence if the stomach of a dog be cut out, and the lower end of the œsophagus sewn to the upper end of the duodenum, it is found that considerable quantities of fat pass undigested through the alimentary canal, since the connective tissue binding fat-cells together can no longer be dissolved by a stomachless dog.

Action on Carbohydrates

The action of the pancreatic juice on starch is similar to that of ptyalin, but is more rapid. It is still further accelerated by the addition of small quantities of bile. The stages of conversion are the same as in the case of ptyalin, the end-products being achroodextrin and maltose. If the action be long continued, the process of hydrolysis may go on to the formation of dextrose, but the amount of this body formed is in all cases very slight, and is probably due to the presence of traces of the special ferment, *maltase*, in the pancreatic juice.

Action on Fats

Fresh pancreatic juice contains a ferment which has a hydrolytic action on neutral fats, splitting them up into glycerin and a free fatty acid, thus:

$$\underset{\text{Tripalmitin (neutral fat)}}{C_3H_5(C_{16}H_{31}O_2)_3} + 3H_2O = \underset{\text{Glycerin}}{C_3H_5(OH)_3} + \underset{\text{Palmitic acid}}{3HC_{16}H_{31}O_2}.$$

This decomposition takes place in the presence of the alkaline salts of the pancreatic juice and bile. The free fatty acid formed by the ferment action combines with the alkali present, displacing the CO_2 to form a soap. The presence of soap in the solution enables it to hold all the rest of the neutral fat in suspension. Thus if a drop of rancid oil (*i.e.* one containing free acid) be allowed to drop on to the surface of a 1 per cent. solution of sodium carbonate, the acid at the exterior of the drop unites with the alkali to form a soap, which is immediately dissolved. The chemical change and solution going on at the surface of the drop set up in the surrounding fluid diffusion-currents which carry off little particles of the neutral fat. These immediately become coated with a layer of soap which prevents them running together again. So we see a white cloud appearing round the drop of rancid oil, and under the microscope the cloud is observed to consist of innumerable tiny droplets of fat suspended in the alkaline liquid. A single shake causes the whole drop to break up into these droplets, the milky fluid thus formed being spoken of as an *emulsion*. In this way the pancreatic juice has the power of emulsifying neutral fats.

This fat-splitting action may go on in a neutral or slightly acid medium, and so is not subject to such restrictions as are the proteolytic or amylolytic functions of the pancreatic juice.

This juice also contains a ferment similar to rennet, which has the property of curdling milk. It is probably of no physiological importance.

SECTION 5

THE BILE

The bile is the product of secretion of the liver. This organ differs in structure from all other glands of the body, the cells being so numerous and pressed together around the capillary meshwork that their primitive arrangement as secreting tubules is no longer to be made out in the adult liver.

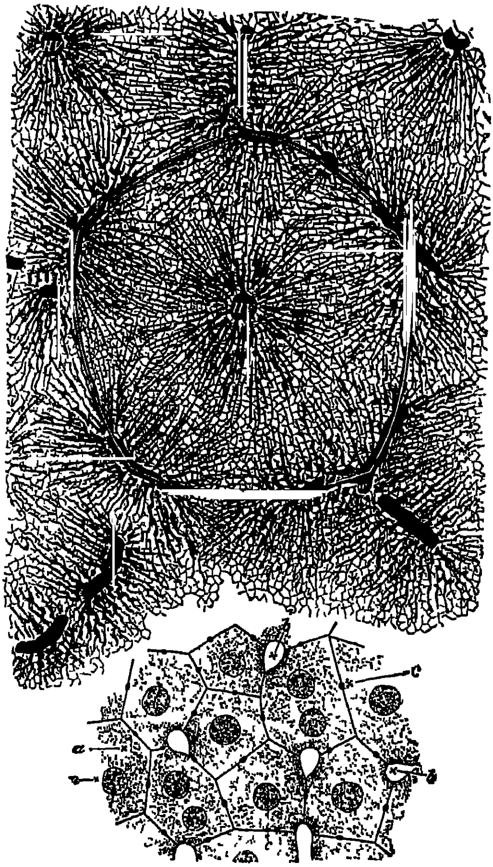
The liver has a double blood-supply · the portal vein, which supplies a rich capillary anastomosis round every liver-cell, and carries venous blood from the alimentary canal; and the hepatic artery, which carries oxygenated arterial blood, and supplies chiefly the connective tissue surrounding the bile-ducts and blood-vessels in the divisions between the lobules, known as Glisson's capsule.

The lobules are about 1·5 mm. in diameter and consist of the liver-cells, blood-vessels, and bile-capillaries, and are bounded by the connective tissue forming Glisson's capsule. The branches of the portal vein run in this connective tissue at the periphery of the lobules, where they are termed interlobular veins. From these veins a rich plexus of capillaries runs towards the centre of the lobule, where they join a small vessel known as the intralobular vein. The intralobular veins unite to form the sublobular veins, which pour their contents into the hepatic veins. These at the hinder border of the liver run into the inferior vena cava, which carries their blood into the heart.

Corresponding with the semi-arterial functions of the portal vein, we find the muscular tissue in its walls better developed than is the case with most veins. The portal vein is also well supplied with vaso-motor nerves, which leave the cord by the lower dorsal roots and run in the great splanchnic nerves. Since the pressure in the portal vein is low (about 10 mm. Hg), any constriction of the portal vein will help to raise the arterial blood-pressure, not so much by increasing the peripheral resistance as by lessening the total capacity of the vascular system.

The whole of the space between the capillaries is filled with liver-cells, which are polygonal in shape, and about 0·02 mm. across. They consist of granular protoplasm with a large

Fig. 174.

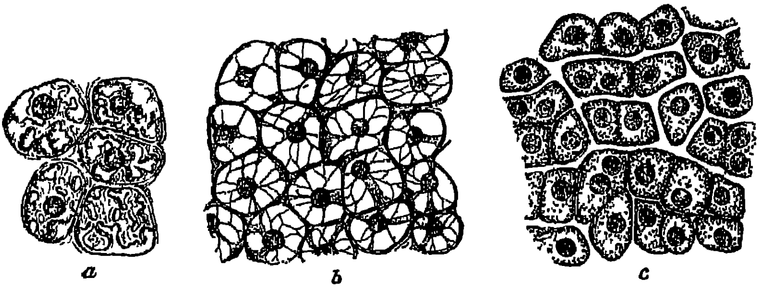


Section of injected liver, showing the division into lobules. The *interlobular* branches of the portal vein (*V P*) are connected with the *intralobular* branches of the hepatic vein (*H V*) by numerous radiating capillaries Below is a portion of the same, more highly magnified *a*, liver cell; *n*, nucleus, *b*, blood-capillaries, *c*, bile-capillaries

rounded nucleus in the centre and may often contain hyaline masses of glycogen (Fig. 175). The bile-ducts, which run at the periphery of the lobules, receive the bile secreted by the liver-cells, by means of a number of very fine branching canals, known as the bile-capillaries. The latter may in section be seen to be situated between the adjacent flat sides of the liver-cells, as far removed from a blood-capillary as possible, their walls being formed by the liver-cells themselves. The bile-ducts join to form the hepatic duct, which leaves the liver at the transverse fissure and passes to the duodenum, giving off on its way a diverticulum, the gall-bladder, connected with the main duct by a special canal, the cystic duct

This subordination of the glandular to the vascular arrangements of the liver betokens a similar subordination of the secreting function of the liver. Although the bile is of importance both as an excretion and as a digestive secretion, its formation represents but a small part of the total activities of the liver, which is the great chemical factory of the body, modifying in the direction of assimilation and dissimilation the various products of digestion brought to it by the portal blood. An animal may survive complete obstruction of the bile-ducts for many months, whereas abolition of the total liver functions is followed by death within a few hours.

FIG 175.



a, hepatic cells containing glycogen, *b*, hepatic cells from which the glycogen has been removed, *c*, a preparation similar to *b*, but from a liver containing originally much less glycogen (Heidenhain)

The secretion of bile is a continuous process, but it does not flow directly into the intestine, being stored up during fasting in the gall-bladder, whence it is discharged by the contraction of this viscus when the acid chyme passes the orifice of the common bile-duct.

The discharge of bile into the intestine is greatest about three to five hours, and again about thirteen hours, after the ingestion of food. The secretion of bile is much quickened by the injection of secretin into the blood stream: a fact that will account for the increased secretion observed within the first few hours after the taking of food. Since bile is an important adjuvant to the pancreatic juice, it is evidently of advantage that its secretion should be increased by the same mechanism that evokes the secretion of the pancreatic juice.

Bile as obtained from the gall-bladder is dark brown or greenish in colour. It is alkaline and slimy from the presence of mucin. Its specific gravity varies from 1010 to 1040. The following table represents the average composition of human bile taken from the gall-bladder.

100 parts contain—

Water	85 parts.
Bile salts	10 ,,
Fats, lecithin, and cholesterin	1 part
Mucus and pigment	3 parts.
Inorganic salts	about 1 part.

Besides these constituents, bile contains gases, especially carbon dioxide, and traces of soaps.

If the bile be collected as it is secreted by the liver, by inserting a cannula in the hepatic duct, it is found to contain a larger percentage of water and little or no mucin. It is evident therefore that during its stay in the gall bladder the bile loses its water, and acquires mucin, which is secreted by the mucous membrane of the gall-bladder.[1]

The bile salts are two in number—*glycocholate* and *taurocholate of soda*. The relative amounts of the two salts vary in different animals, the taurocholate being as a rule most abundant in carnivora, and the glycocholate in herbivora. In human bile, glycocholate forms nearly the whole of the bile salts present.

The bile salts may be extracted in the following way:—Bile is mixed into a paste with animal charcoal, and the mixture dried, pounded up, and extracted with absolute alcohol and filtered. On adding ether to the alcoholic filtrate, and allowing it to stand, a crystalline precipitate is produced, consisting of the two bile salts. These have a bitter taste, and are easily soluble in water. Their presence in a fluid may be shown by *Pettenkofer's reaction*.

---

[1] The greater part of the mucin-like substance occurring in ox bile, and precipitated by acetic acid, is really a nucleo-albumen. Human bile on the other hand contains true mucin

Addition of a drop of cane-sugar solution and excess of concentrated sulphuric acid to a solution of bile salts gives a purple colour, due to the interaction of *furfurol*, produced by the action of the sulphuric acid on the cane-sugar, with cholalic acid, the common constituent of both bile acids. This colour may be interfered with by the dark-brown colour produced by the charring of the sugar with the sulphuric acid Either of the following ways may be adopted to obtain a good purple reaction

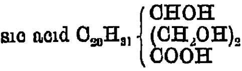
A The bile and sugar are shaken up in a test-tube until the upper part of the tube is filled with froth If the concentrated sulphuric acid be now poured down the side of the tube, the froth is stained a purple colour where it comes in contact with the acid

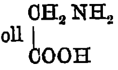
B A porcelain capsule is rinsed out successively with solutions of bile salts, cane sugar, and dilute sulphuric acid (25 per cent) On warming the capsule gently over a flame, water is driven off from the thin film of dilute acid, and the concentrated acid thus produced acts on the thin film of sugar and bile salts, causing a brilliant purple colour of the whole of the inner surface of the capsule

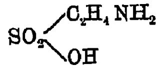
Glycocholic acid is a conjugated acid, which on hydrolysis splits up into glycine (amido-acetic acid) and cholalic acid ($C_{24}H_{40}O_5$).

Taurocholic acid is also a conjugated acid, which can be split up into taurine, an amido-acid containing a large proportion of oxidised sulphur (amino-isethionic acid), and cholalic acid.

The glycocholic acid can be obtained from the bile of some herbivora in a free condition by adding a little hydrochloric acid and ether and shaking, when the acid crystallises out in fine needle-shaped crystals

Cholalic acid is a monobasic acid  $C_{20}H_{31}\left\{\begin{array}{l}CHOH\\(CH_2OH)_2\\COOH\end{array}\right.$, and is obtained from either bile acid by prolonged boiling with strong solution of caustic soda Under the influence of acids or putrefaction (as in the intestine) it is converted into an insoluble anhydride, known as *dyslysin*

Glycine or glycocoll  $\begin{array}{l}CH_2\,NH_2\\|\\COOH\end{array}$ is also obtained by the hydrolytic dissociation of some proteins and of certain albuminoids such as gelatin and elastin. It occurs in the urine conjugated with benzoic acid as hippuric acid

Taurine  $SO_2\begin{array}{l}\diagup C_2H_4\,NH_2\\\diagdown OH\end{array}$ is found nowhere else in the body, and is the only known example of a sulphonic acid which plays any part in the normal functions of the body. It can be formed artificially from cystine, a normal constituent of all proteins.

The mucin and nucleo-albumen present may be precipitated by acetic acid. The precipitate is soluble in dilute alkalies.

The bile-pigments are *bilirubin* (brown) and *biliverdin* (green), and occur in the bile in combination with calcium. The colour of the bile depends on the relative amounts of these two pigments present. Biliverdin ($C_{16}H_{18}N_2O_4$) may be obtained on oxidation of bilirubin ($C_{16}H_{18}N_2O_3$).

The presence of bile-pigments may be proved by *Gmelin's test*. A drop of bile on a white plate is treated with a drop of yellow nitric acid. Where the two drops come in contact a play of colours is produced, due to the formation of various oxidation-products of bilirubin. These colours occur in the following order—brown, green, blue, red, yellow. The end-product of the reaction which gives the yellow colour is known as *choletelin*.

The cholesterin present is probably kept in solution by the bile salts. Under abnormal conditions, cholesterin may be precipitated and may form concretions in the gall-bladder (gall-stones). More rarely we meet with gall-stones consisting of the bile-pigments in combination with alkaline earths.

Actions of Bile

Bile contains small quantities of an amylolytic ferment which has a feeble digestive action on starch. If added to a mixture of starch and pancreatic juice, it materially hastens the action of the latter.

On adding bile to an acid solution of albumoses and peptones, such as the products of gastric digestion which come through the pylorus into the first part of the duodenum, a precipitate is produced, consisting of glycocholic acid, syntonin, and albumoses.

One function of the bile then is to neutralise the gastric juice and prepare the way for pancreatic secretion.

The alkaline salts of the bile can combine with the fatty acids set free by the pancreatic juice to form soaps, and so aid in the digestion and emulsification of fats. Bile also assists in the absorption of fats by virtue of the bile salts it contains. Oil will not run through a filter moistened with water, but will do so if it be moistened with a solution of bile salts. The presence of bile salts lowers the surface-tension between the oil and the water, so that in the intestine the droplets of fat are able to come into intimate contact with the absorbing surface of the epithelium, and with the digestive fluids.

The main importance of the bile however is as a fat solvent. In a slightly acid medium the bile acids will dissolve 4 to 5 per cent. of free fatty acid. Bile has no solvent action on neutral fats, but will dissolve soaps, including the insoluble soaps of the alkaline earths. The importance of bile for the absorption of fats is shown by the occurrence of a large amount of undigested fat in the fæces on shutting off the bile from the intestine. The fat-solvent action of the bile salts in the bile is much aided by the simultaneous presence in this fluid of lecithin and cholesterin in solution.

The presence of bile in the intestine is said to excite contractions of the muscular walls, and so act as a natural purgative. In the same way the muscular fibres of the absorbent villi are stimulated by the presence of bile, and contract, forcing the contents of the villus into the subjacent lacteal.

Bile is often spoken of as an antiseptic, but this statement must be qualified. The free bile acids, especially taurocholic acid, have a pronounced antiseptic action. The action is however lost when the acids are combined with alkalies, as in the bile itself, which decomposes extremely readily.

The Origin and Fate of the Biliary Constituents

The bile is to be regarded partly as a secretion, having an important function in the digestion of fats, and partly as an excretion—a means by which the effete colouring matter of the blood is got rid of.

The bile salts are formed by the liver, as is shown by the fact that, after extirpation of the liver in frogs or birds, no accumulation of these salts takes place in the body If however the bile-ducts be ligatured, bile salts are found in the blood and in the urine. The glycine and taurine are probably derived from protein disintegration, but we know nothing concerning the precursors of cholalic acid. In the intestine the bile salts play their part in the digestion of fats, and are then for the most part reabsorbed, passing along the portal vessels to the liver, where they are again secreted, so that they can exert their functions over and over again. A certain amount is split up in the intestine into the amino-acids and cholalic acid, the former being reabsorbed, and the latter being excreted with the fæces.

The bile-pigments are the products of disintegration of the hæmoglobin of the blood. They play no further part in the body, and are excreted with the fæces in a slightly altered form. It was long debated whether they were formed by the liver, or whether some might not be formed in the blood itself or in the other tissues from the disintegrated red corpuscles. ? It is found that, after blood has been extravasated into the tissues, the hæmoglobin undergoes certain modifications, and is converted into the body named hæmatoidin. Now hæmatoidin is isomeric and probably identical with bilirubin, and this fact was looked upon as furnishing strong evidence for the hæmatogenous origin of bile-pigments. Experiment has shown however that when blood-corpuscles are broken up in the circulation (a process which is normally taking place on a small scale) no bile-pigment is formed except by the agency of the liver. A great breaking-up of blood-corpuscles and setting free of hæmoglobin may be caused in animals by the inhalation of arseniuretted hydrogen. If the liver be present, this disintegration of blood-corpuscles causes a greatly increased formation of bile-pigment, which is eliminated with the bile, or partly reabsorbed by the lymphatics from the biliary passages, giving rise to jaundice. If in a goose the liver be shut out from the circulation or extirpated, and arseniuretted hydrogen administered, not a trace of bile-pigment is produced.

The cholesterin of the bile is sometimes looked upon as a product of nerve-disintegration, since this substance is found abundantly in the central nervous system; but we have no evidence for or against this view.

Bile is secreted at a very low pressure—15 mm. Hg. If the pressure in the bile-ducts rises above this point, as may easily happen when the flow is obstructed in consequence of inflammatory thickening of the mucous membrane, or by the presence of a gall-stone, or even by a very viscid bile, the bile is reabsorbed by the lymphatics and reaches the blood, and nearly all the tissues of the body are stained yellow by the pigments, giving rise to jaundice. This pressure however is higher than the pressure in the portal vein, which is only about 10 mm. Hg; for we must remember that the blood in the portal vein has already passed through a system of capillaries, so that its pressure is extremely low. The fact that the pressure in the bile-ducts may exceed that in the portal vein shows that the secretion of the water of the bile is not effected by a mere process of filtration.

Section 6

SUCCUS ENTERICUS OR INTESTINAL JUICE

univ. Q

The secretion of the tubular glands (Lieberkuhn's follicles), which beset the mucous membrane of the intestine, may be obtained in a pure condition in the following way. An opening is made into the abdomen of an animal, and a piece of the small intestine, ten or twelve inches long, is separated from the rest, its attachment to the mesentery with its blood-vessels and nerves being left intact. The two ends of the remaining piece of intestine are sutured together, so that the animal is left with a continuous but shortened alimentary canal. One end of the excised piece is closed by sutures, and the margins of the other end sewn to the margins of the abdominal wound. An intestinal fistula is thus produced, from which the juice may be collected free from contamination by the other digestive juices. Secretion is normally excited by the mechanical stimulation of the food as it passes down the intestine, and may be evoked in the isolated loop by the introduction of a rubber balloon. The presence of pancreatic juice is said also to act as a specific stimulus for the intestinal glands. The amount of succus entericus to be obtained in either of these ways varies very much according to the position in the intestine of the isolated loop. Thus a large secretion is obtained from an isolated loop of the upper part of the intestine including the duodenum, and it is stated that in this situation secretion may be excited by the intravenous injection of *secretin.* If, however, a loop be made from the lower end of the ileum, it is difficult to obtain even a few drops of intestinal juice, whatever form of stimulation be employed.

Intestinal juice is a clear, limpid fluid, with a specific gravity of 1010, containing a trace of protein, and salts, of which sodium carbonate is the most abundant. In consequence of the presence of this salt it has a strong alkaline reaction.

Actions

On coagulable proteins, fats, and starch, succus entericus has no action. It contains however invert ferments, by the agency of which cane-sugar is converted into dextrose and laevulose, and maltose is converted into dextrose. Lactase, which converts milk sugar into galactose and dextrose, is often present, and is always found in animals on a milk diet. The important 'ferment of ferments' *enterokinase*, which awakens the proteolytic activity of the pancreatic juice, has already been mentioned. The alkaline reaction of the succus is probably important in neutralising the free acids (lactic, butyric, etc.) produced by the action of putrefactive micro-organisms on the foodstuffs. Although intestinal juice has no action on coagulable proteins, it contains a ferment, *erepsin*, which converts the albumoses and peptones, produced higher up in the gut, into the amino-acids and hexone bases which are the final products of the action of trypsin on proteins.

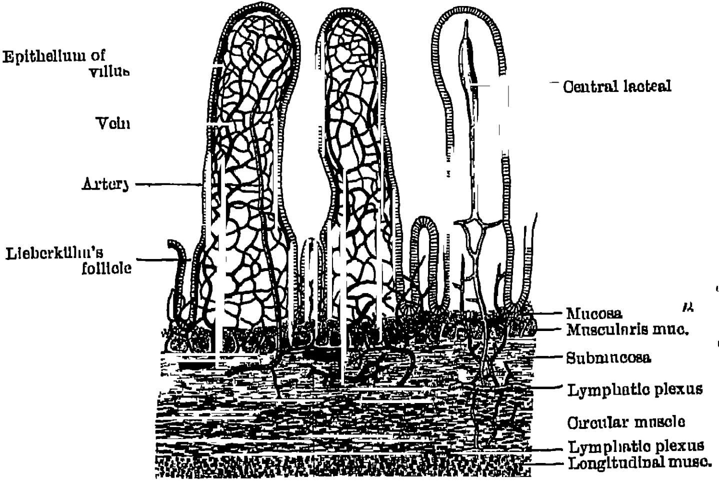
The following experiment is supposed to show the influence of the intestinal nerves on the secretion. The abdomen being opened, the small intestine is ligatured in four places, so as to shut off three equal lengths of bowel; all the nerves going to the middle segment are divided and the abdomen closed. At the end of two or three hours the wound is opened, and it is found that the middle segment is distended with fluid, whereas the other two segments, which have their nerves intact, are comparatively empty. This secretion has been regarded as analogous to the paralytic secretion of saliva, which continues for some weeks after section of all the nerves going to the submaxillary gland. We do not know however how far this phenomenon is to be ascribed to vascular changes taking place in the loop of intestine in consequence of the section of its nerves.

SECTION 7

ABSORPTION OF FOODSTUFFS

We must now consider the ways in which the foodstuffs, that have been digested and rendered soluble in the alimentary canal, pass into the circulation to be distributed to all the cells of the body. There are two main paths of absorption—the blood-vessels and lymphatics. The blood-vessels form a dense capillary anastomosis immediately under the epithelial layer covering the inner surface of the mucous membrane. In order to increase the absorbing surface, the mucous membrane of the small intestine in man is thrown into transverse folds—the *valvulæ conniventes*, which are thickly covered with finger-like elevations or villi. The body of a villus is made up of a reticular tissue composed of branching cells, the meshes of which may contain leucocytes of various forms. In the centre of the villus is a wide lymphatic vessel, the central lacteal. The endothelial cells

FIG 176



Diagrammatic section through wall of small intestine to show vascular and lymphatic arrangements of mucous membrane (From Böhm and Davidoff, after Mall) forming the wall of the lacteal are continuous with the branched cells of the reticular tissue, but there is no free communication between the spaces of this tissue and the beginning of the lymphatic. Below, the cavity of the lacteal is continued into a plexus of lymphatics lying in the mucous membrane, which communicates by vertical branches with a large plexus lying in the submucosa. The intestinal surface of the villus is covered with a single layer of columnar epithelial cells, which have a hyaline border presenting delicate vertical striation, apparently due to the presence in the border of a number of cilia-like processes The capillary network lies outside the lacteal immediately under the epithelium. The blood-vessels pour their contents into the radicles of the portal vein, which carry them thence to the liver. The lymphatics in the submucosa join to form larger trunks, which run between the two layers of the mesentery to a collection of lymphatic glands at the back of the peritoneal cavity. The lymph, after flowing through these glands, is collected into a large vessel—the *receptaculum chyli,* from which it is carried in the thoracic duct to be discharged into the blood-stream at the junction of the left jugular and subclavian veins.

Absorption of Fats

During fasting the lymph contained in these vessels is exactly similar to that contained in any other part of the body. If a cannula be inserted in the thoracic duct of a fasting dog, and the animal be given a meal rich in fat, it is found that the amount of lymph flowing from the cannula is the same as before, but the lymph has changed its appearance, being now white like milk. On microscopic examination this milky appearance is found to be due to the presence of small fatty globules similar to those in milk, and of a number of very fine particles—much finer than any of the globules met with in milk—which may exhibit Brownian movement. These constitute the 'molecular basis' of the chyle. If the abdomen of the animal be opened, the course of the lymphatics along the mesentery is evident from the milky character of their contents. It is on account of this milky appearance during digestion that the name of lacteal has been given to the lymphatics of the alimentary canal; and chyle is simply lymph with fatty globules, and molecular basis.

Since the whole of the chyle is poured by the thoracic duct into the blood, the plasma or serum of the latter, obtained after a meal containing fat, is also found to present a milky appearance, in consequence of the presence of fat globules derived from the chyle. If however the thoracic duct be ligatured, a fatty meal is not followed by any increase in the amount of fat in the blood.

It is apparent then that the greater part of the fat is absorbed by the chyle, and 60 per cent. of the absorbed fat can be obtained from the chyle through a cannula placed in the thoracic duct. Comparative analyses of portal and carotid blood during digestion show that the amounts of fat contained in the two are the same; hence it is concluded that no fat is absorbed through the intermediation of the blood-vessels. It has not yet been found possible to trace the mechanism of absorption of that portion of the fat which does not enter the blood by way of the lacteals. It is possible that it may be utilised or built up into more complex compounds in the tissues of the intestinal mucous membrane.

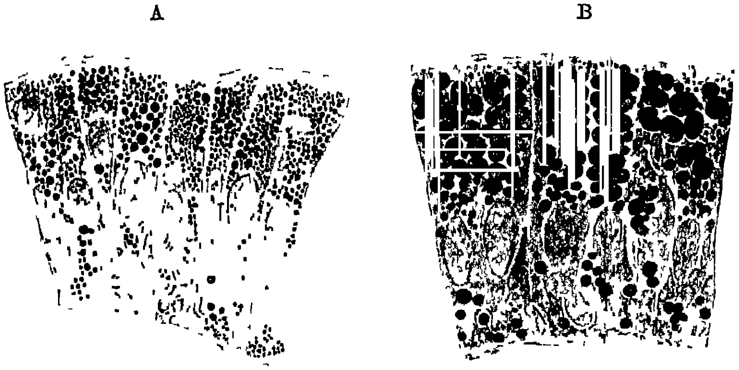
We must now inquire how the fat gets into the lacteals. If sections be made of the villus during the digestion of fat, and stained with osmic acid, the epithelial cells are seen to be full of black fatty granules of various sizes (Fig. 177). These granules are also to be observed in the spaces surrounding the central lacteal.[1] The lacteal itself is full of lymph with fat-globules, but the latter are here much more minute, and correspond to the molecular basis of the chyle.

We must conclude that the fat is taken up by the epithelial cells covering the villus. But in what form? We have already seen that the effect of the pancreatic juice on neutral fats, which form the great proportion of the fat of food, is to split them up to a certain extent into free fatty acid and glycerin. The rancid fat thus produced in an alkaline medium at once forms an emulsion, and since the chyle also contains fat in a finely divided condition, it was thought that the digestion of fat essentially consisted in a splitting up into particles fine enough to be taken up by the epithelial cells. On examining sections of the villi during fat-absorption, it will be seen however that the striated border is always free from fat-globules, and that the globules grow in size from the inner to the attached border of the cell. Moreover by such an explanation it is difficult to account for the extreme importance of bile for the absorption of fat. It seems practically certain that there is no fundamental difference between the absorption of fats and that of carbohydrates and proteins, and that they are all alike absorbed in a state of solution. If fatty acids are administered to an animal they are absorbed, but appear in the chyle as neutral fat, showing that a synthesis of the fatty acid and glycerin has taken place on the passage of the fatty acid from the intestine to the lacteal through the epithelium. In the same way, soaps taken with the food appear in the chyle as neutral fats, and in both cases the assimilation is improved by the addition of the necessary amount of glycerin. We may conclude that the formation of an emulsion in the intestine is not the end of the digestive

---

[1] Many of the leucocytes also present black granules, but these are supposed not to be of a fatty nature, since they are not dissolved on treating the section with ether.

FIG. 177.



Columnar epithelium from small intestine of frog stained with osmic acid to show fat-absorption A, five hours after a meal of olive oil; B, three hours later. It should be noticed that the fat globules first formed grow in size in the course of digestion, pointing to a gradual deposition of fat on the globules from solution in the protoplasm.

process, but serves merely to bring a larger surface of the fat in contact with the digestive juices. In the digestion and absorption of fat there is a concerted action of the pancreatic juice and the bile. The pancreatic juice splits about 6 per cent. of the neutral fat into fatty acid and glycerin. In the presence of excess of alkalies, the fatty acid forms a soluble soap which, together with the glycerin, is absorbed by the epithelial cells, and recombined in the body of the cell into neutral fat. If, as is often the case especially with a highly fatty diet, the reaction of the small intestine be acid, the formation of soaps can no longer go on. The fat-splitting action of the pancreatic juice however continues, and the fatty acids set free are dissolved by the bile acid and taken up by the epithelial cells. Here the synthesis of the neutral fat once more occurs, and the bile acid is carried by the portal blood to the liver to be re-secreted with the bile into the intestine, where it may aid the absorption of a further amount of fat. As the free fatty acids and soaps are absorbed, the pancreatic juice is able to split up a further portion of the neutral fat, until the whole of the neutral fat of the food has been absorbed by the epithelial cells of the intestine in a state of solution as soaps or fatty acids. It is partly on this account that, after extirpation of the pancreas, fats are not absorbed even if administered to the animal in the form of a fine emulsion containing neutral fat suspended in a solution of soap. If however to this emulsion chopped-up pancreas be added, a large proportion of the fat is absorbed.

The epithelial cells extrude the fat-granules into the spaces of the reticular tissue. Here a certain amount may be taken up by the leucocytes and carried into the beginning of the lacteal. The greater proportion however is probably pressed forcibly through the wall of the central lacteal by the contractions of the muscular tissue of the villus. A further contraction of these fibres empties the lacteal into the submucous plexus of lymphatics, where the presence of valves prevents any reflux, so that, on relaxation of the muscle-fibres, there is no hindrance to the further passage of fat and lymph into the flaccid central lacteal. This is the so-called pumping action of the villus.

Absorption of Carbohydrates

The other constituents of the foodstuffs seem to be absorbed chiefly, if not completely, by the blood-vessels. Blood normally contains a small amount of dextrose (0·1 to 0·2 per cent.), and the proportion of sugar in the lymph is the same as in the blood. After a meal rich in carbohydrates, the proportion of sugar in the chyle flowing from the thoracic duct is the same as that in the blood from the carotid artery; but it is found that there is slightly more sugar in the blood from the portal vein than in that from the hepatic vein or carotid artery. It is inferred therefore that the blood in the capillaries of the intestinal wall takes up sugar in the form of dextrose and carries it to the liver. Here the excess of sugar is taken up by the hepatic cells, and converted by them into the colloid carbohydrate, glycogen, which is deposited in the substance of the cell. In this way the liver acts as a storehouse of carbohydrate material, and prevents the sugar in a rich carbohydrate meal from escaping into the general circulation. This function is important, since it is found that if the amount of sugar in the blood be raised above the normal, the excess is immediately excreted by the kidney; so that without such an economising organ as the liver the greater part of a carbohydrate meal would at once be wasted.

We have already seen (p. 336) that the end-product of the action of the salivary and pancreatic ferments on starch is a mixture of maltose and achroodextrin. In the blood of the portal vein however, we find only dextrose; and it appears that the dextrin and maltose must undergo some further change before reaching the blood. We know for certain that the succus entericus contains a ferment which can convert maltose into dextrose; but it is possible also that the epithelial cells lining the intestine are able to effect a transformation of both dextrin and maltose into dextrose. It must be remembered too that normal blood-plasma, serum, and lymph contain a ferment which quickly converts boiled starch, glycogen, dextrin, or maltose into dextrose. At any rate under normal circumstances no dextrin or maltose is to be found in the blood of the portal vein or in the chyle, although these substances are absorbed from the intestine.

Absorption of Proteins

Proteins are for the most part converted into peptones and albumoses before absorption. This absorption takes place by means of the blood-vessels. Thus a large protein meal is as readily absorbed in a dog whose thoracic duct is ligatured as in a normal dog. A large protein meal always gives rise to a marked increase in the amount of urea excreted in the urine, and this increase is found also in a dog whose thoracic duct has been ligatured, showing that the protein has been absorbed and distributed through the whole system.

If however we analyse the blood of the portal vein during active protein digestion, not a trace of peptone is found. Injection of even small quantities of albumoses or peptone into the portal vein or any part of the blood-stream gives rise at once to peptonuria, and the greater part of the peptone injected reappears in the urine, from which it can be collected. Thus it is impossible that the proteins can reach the blood-stream in the form of peptone, and the following experiments have been interpreted as showing that peptone is regenerated into coagulable protein in its passage through the epithelial cells of the alimentary canal

A piece of the mucous membrane of the stomach during active protein digestion is excised and divided into two pieces. One piece (A) is thrown at once into boiling water, and the other piece (B) is allowed to remain for three hours in a warm moist chamber at 40° C., and is then plunged into boiling water. On analysing the two pieces a large amount of peptone is found in A, whereas in B the merest trace or none is present. During the stay in the warm chamber, all the peptone in B has been converted into something else, probably coagulable protein. That this action presumably depends on the vital activity of the epithelial cells and not on unorganised ferments present in the cells, is shown by the fact that plunging the membrane into water at 60° C. is as efficacious in stopping the action as when water at 100° C. is used. At 60° C. all living cells in the body are destroyed, but not all unorganised ferments.

The following experiment also points to a total disappearance of the peptone during absorption.—A loop of a dog's intestine is excised, its contents washed out with a normal saline fluid, one gramme of peptone placed in it, and the ends ligatured. Dilute defibrinated blood is now passed for two or three hours through the vessels supplying the loop in order to keep it alive. At the end of this time, on cutting open the loop, all the peptone is found to have disappeared, and on analysis of the blood that has passed through the vessels of the loop, no peptone can be found. It was therefore concluded that peptone had been converted into a coagulable protein in its passage through the absorbing epithelium.

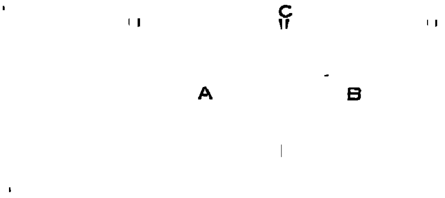
More recent investigations by Leathes and others have, however, tended to put a different interpretation on these results. The mucous membrane of the whole alimentary canal contains erepsin, and the disappearance of peptone can be equally well explained on the assumption that it has been entirely converted by this ferment into amino-acids and other substances, which no longer give the biuret reaction typical of albumoses and peptones. It is true that so far observers have failed to obtain any increase in the nitrogenous extractives of the portal blood during digestion, but the circulation through the vessels of the gut is so rapid that the whole of a large protein meal might be absorbed in the form of these nitrogenous extractives without giving such a rise in the amino-nitrogen of the blood as to be detectable by our means of analysis.

On the other hand, it is not necessary that the protein should be all peptonised before being taken up by the epithelial cells. It has been shown that protein, such as egg albumen or acid albumen, may be absorbed by an isolated loop of bowel or by the lower end of the large intestine, which has been washed free from any trace of proteolytic ferment that may have been carried down to it from the pancreatic juice. Peptonisation however helps the work of the epithelial cells, and materially hastens the process of absorption. It is probable that a large proportion of the proteins of the food may undergo complete disintegration into amino-acids and bases, being absorbed in these forms into the blood, and built up again into proteins in the living cells of the tissues, the extent to which any individual protein is broken down during digestion being determined by the degree in which its composition approximates to that of the normal proteins of the digesting animal.

Absorption of Water and Salts

Owing to the simple character of the factors involved, the study of the absorption of water and salt solutions from the intestine is of considerable importance for the problem of the mechanism of absorption generally, since it enables us to determine whether the absorption is effected along purely mechanical lines or whether the cells lining the intestine take an active part in the process. On the latter hypothesis we should regard the process as one of inverted secretion. Whereas in glands the secretory epithelium takes up substances from the lymph and turns them out with more or less modifications into the lumen of the alveoli, in the intestine the epithelium would take up the food material and products of digestion and excrete them in a more or less changed condition on the other side into the lymph- and blood-spaces of the villus.

FIG 178.



We may first consider the physical factors which would influence the passage of water and dissolved substances across the intestinal epithelium. In the case of two compartments A and B, separated by a permeable membrane C, an interchange of material will go on so long as there is any difference in the chemical composition on the two sides. If the proportion of a dissolved substance such as sodium chloride, be greater in A than in B, the movement of salt from A to B will preponderate over that from B to A. If the total number of dissolved molecules be greater in A than in B, the osmotic pressure in A will be greater than the osmotic pressure in B, and there will consequently be a flow of water from B to A. In the case of substances of different diffusibility, the less diffusible substance will exert at first more osmotic pressure than the more diffusible, so that if equimolecular solutions of sugar and sodium chloride be taken, the fluid will move from the sodium chloride side on to the sugar side at a greater rate than in the reverse direction; and the volume of the sugar-solution will increase at the expense of the sodium chloride. It is evident that if the membrane be partially or completely impermeable to certain substances, these substances will have a greater effective osmotic pressure and so be instrumental in determining an absorption towards their side. Where however the fluids on the two sides are identical, no property of the membrane will effect a transference from one side to the other, nor can any specific permeability cause the passage of a dissolved substance, so to speak, uphill, *i.e.* from a position of lower to a position of higher partial tension. On investigating the absorption of saline fluids from the intestines in the light of these principles, we find that, although absorption is influenced by the concentration and composition of the fluids within the intestine, yet these physical factors are not the only nor the chief determinants in the process, but that the living cells of the mucous membrane play an important part in choosing and actively passing on certain constituents of the food. If we take a solution of a salt, such as sodium sulphate, the question seems at first sight a purely physical one, a hypertonic [1] solution being increased in amount, while a hypotonic solution is concentrated by the absorption of water, until its molecular concentration is the same as that of the blood serum. If however we make use of the more physiological solutions, such as dextrose or sodium chloride, we find that these substances are absorbed rapidly from weak or from strong solutions, the rate of absorption being apparently very little influenced by the diffusibility of the substance in question. We can in fact represent absorption as made up of two factors, the physical and the physiological. Where they are in opposition, absorption goes on slowly and represents work done on the fluid by the absorbing cells. We may abolish this physiological factor by the addition of such substances as sodium fluoride to the solutions, by which means we poison the cells without apparently altering the sistence of the membrane. By a twisting of hypotheses, aight be possible to explain even these facts without urse to a physiological factor, but it is impossible to lain in this way the absorption of substances such as um or solutions of egg albumen, containing indiffusible oids in solution, and in the former case identical in all ects with the serum circulating in the blood-vessels of villi.

---

[1] A *hypertonic* solution is one that is more concentrated than normal fluids, such as serum or normal NaCl solution A *hypotonic* fluid is less concentrated than a normal fluid.

We have already met so many examples of an activity of intestinal epithelium, such as the re-synthesis of fats, the neration of peptone, and the passage by some means or r of the regenerated coagulable protein into the blood-sels of the villi, that it is not strange to find the cell also ng for the absorption of such necessary constituents of food as salts and sugars. Where the salts are of small no physiological importance, the cell in many cases ears to have no power of physiological absorption, and salts exert their full physical influence, absorbing water retaining that by which they are dissolved, so that they as saline purges, *e g.* sodium or magnesium sulphate.

The rate of absorption of water by the alimentary canal eases from above downwards. No water or dilute saline tions appear to be absorbed by the stomach. If a denal fistula be established, as much fluid will be dis-rged by the fistula as is administered to the animal by the th. In the small intestine, the process of absorption is h more rapid in the ileum than in the jejunum. In sequence however of the continual secretion of the succus ricus, the intestinal contents reach the ileo-colic valve in uid condition, and the excess of water is only absorbed in large intestine.

This difference in the absorbing power of different parts of gut has reference chiefly to water. Dissolved substances, h as alcohol, dextrose, alkaloidal poisons, are absorbed with eme rapidity from the stomach as from all parts of the gut.

Water and salts are absorbed almost entirely by means he blood-vessels. If a cannula be placed in the thoracic t, little or no increase of the flow is obtained even during absorption of large quantities of salt solutions from the stine.

SECTION 8

Imp

SUMMARY OF THE CHANGES UNDERGONE BY THE FOOD IN THE ALIMENTARY CANAL

In the mouth the food is broken up into small particles by mastication, and moistened with alkaline saliva, in order to fit it for deglutition. A small part of the starch is converted into dextrin or maltose.

On reaching the stomach the action of the saliva may go on for thirty to sixty minutes. At the end of this time the secretion of gastric juice, excited by the presence of food and of alkaline saliva in the stomach, is sufficiently abundant to neutralise and render acid all the gastric contents, and so stop the action of the ptyalin. Under the action of the gastric juice the greater part of the protein is dissolved, and converted into syntonin, albumoses, or peptones. The connective tissues are also dissolved, setting free the fat, which floats about in a free state. At the same time some of the salts and sugar which have been swallowed, and the peptones formed from the food, are being absorbed by the gastric mucous membrane. For the first half-hour after ingestion of a meal of solid food, the pylorus is firmly closed. At the end of this time it relaxes at intervals to allow the passage of the fluid parts of the gastric contents, which are spoken of at this period as *chyme*. The passage of food through the pylorus goes on for seven or eight hours after the ingestion of food, and towards the end of this time larger lumps of undigested material are allowed to pass on into the duodenum.

As the acid chyme is squirted through the pylorus into the duodenum, it comes into contact with the cells of the mucous membrane, and in them causes a conversion of prosecretin into secretin. The latter is absorbed by the blood stream and carried to the pancreas and liver, causing a flow of pancreatic juice and an increased secretion of bile. The strongly alkaline pancreatic juice neutralises the acid chyme. So long as the duodenal contents are acid, the pylorus remains closed, but opens as soon as sufficient pancreatic juice has been secreted to neutralise the chyme that has already passed through. When this happens the pylorus relaxes, a fresh quantity of acid gastric contents is forced through, more secretin is formed, and the pancreatic secretion is again excited until the second amount of chyme is neutralised; and this self-steering regulation of the activities of the stomach, pancreas, and intestines goes on until all the food has passed through the pylorus. At the same time the pancreatic juice poured into the gut evokes a secretion of succus entericus, which supplies the enterokinase necessary for the activation of the proteolytic ferment of the pancreatic juice.

In the duodenum the chyme comes in contact with the bile, the flow of which is also quickened under the influence of the secretin which is being poured into the circulation. This causes a precipitate in the chyme, consisting of bile acids, syntonin, and albumoses. This precipitate is dissolved later on by the further operation of the pancreatic juice. Here the remaining digestive processes take place; the undigested proteins are dissolved, and the acid albumen and albumoses resulting from gastric digestion are converted into peptone and partially into leucine, tyrosine, and similar nitrogenous bodies. Starches are changed into maltose and dextrin, and, under the further agency of the intestinal juice, into dextrose. The fats are partially split up and emulsified.

Throughout the whole of the small intestine active secretion and absorption are taking place, so that the amount of water in the intestinal contents in the lower part of the small intestine is about the same as in the upper part. The contents of the lower part acquire a distinct fæcal odour from the indol and skatol produced by the action of putrefactive bacteria on the tryptophane contained in the proteins of the food. In the large intestine the processes of absorption predominate over those of secretion, hence that part of the intestinal contents which has not been absorbed becomes less and less watery, and acquires the character of fæces, in which form it is periodically expelled from the body.

The fæces consist mainly of the indigestible residue of the food, or of substances which have been taken in too large quantities to be digested, and contain—

(*a*) Cellulose, woody fibre, elastic tissue, keratin, and remains of muscle-fibres, starch-grains, and fat.

They also contain—

(*b*) The unabsorbable part of the digestive juices, such as mucin, altered cholalic acid (*dyslysin*), bile-pigments, cholesterin.

(*c*) Indol and skatol, various forms of bacteria, and disintegrated epithelial cells from the intestinal mucous membrane.

(*d*) Certain products of excretion of the intestinal mucous membrane. Many metallic poisons (*e.g.* iron, mercury) are excreted into the cavity of the intestine and leave the body in the fæces as sulphides of the metals.

SECTION 9

MUSCULAR MECHANISMS OF DIGESTION

Mastication

By movements of the lower against the upper jaw, the food is crushed between the teeth and reduced to a finely subdivided condition to fit it for the action of the various digestive fluids. The lumps of food are continually pushed between the teeth by movements of the tongue, cheek, and lips. The whole act is voluntary, although it is associated with and rendered easier by the saliva which is poured out into the mouth at the same time, and the secretion of which is excited reflexly.

The nerves supplying the muscles engaged in mastication are the fifth nerve (to jaw muscles), facial, and hypoglossal.

Deglutition

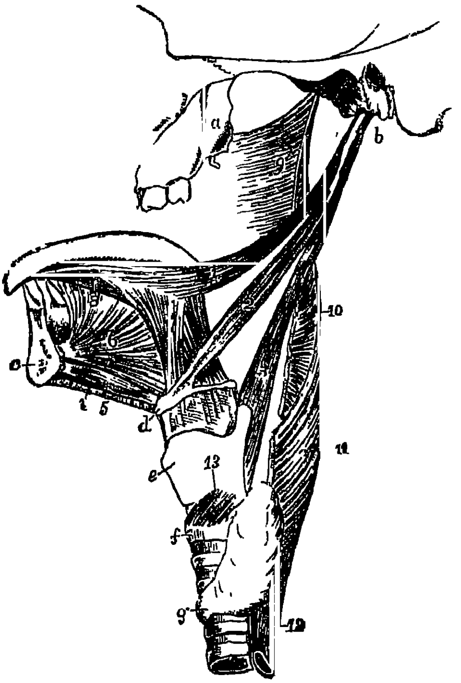
When the food is sufficiently subdivided, it is gathered by movements of the tongue against the hard palate into a bolus which rests on the dorsal surface of the tongue, whence it is propelled through the fauces into the œsophagus.

The movements of deglutition may be divided into three stages.

In the first stage the bolus is carried by the tongue through the isthmus faucium. This act is voluntary. As soon as the bolus has passed the isthmus, it is in a region common to the food and respiratory processes.

Here, by a series of rapid reflex movements, constituting the second stage, it is sent on into the beginning of the œsophagus. The movements are as follows —The levator palati draws the soft palate upwards and backwards, and this with the contracted palato-pharyngei entirely closes the nasal cavities. At the same time the intrinsic muscles of the larynx contract, closing the rima glottidis by approximating the vocal cords while the entire larynx is drawn up behind the hyoid bone by the thyio-hyoid muscle, and the superior opening of the larynx is closed by the approximation of the arytænoid cartilages to the base of the tongue and the epiglottis. Then by the contraction of stylo-pharyngei and palato-pharyngei the upper part of the pharynx is drawn like a glove on a finger over the bolus of food, which is grasped by the superior constrictor, and passed on from this to the middle and inferior constrictors of the pharynx.

Fig. 179



Dissection to show muscles employed in deglutition *b*, styloid process, from which arise 1, the styloglossus, 2, the stylohyoid, 3, the stylo-pharyngeus muscles, *c*, section of lower jaw, *d*, hyoid bone, *e*, thyroid cartilage, *g*, isthmus of thyroid gland; 4, cut edge of mylo-hyoid muscle, 5, 6, 7, 8, muscles of tongue, 9, 10, 11, superior, middle, and inferior constrictors of pharynx; 12, œsophagus (Allen Thomson)

The third or œsophageal stage is slow and entirely involuntary. The bolus is forced down the œsophagus by a peristaltic wave of contraction passing down the muscular walls of this viscus.

The propagation of this contraction from one segment of the œsophagus to the next is a reflex act. Section of the vagus branches to the œsophagus arrests the wave, although it is not checked by section of the œsophagus itself. A peristaltic contraction is not necessary in most cases to secure the carrying of food to the stomach. If a series of acts of deglutition be made at intervals of a second, no peristaltic wave of contraction takes place till after the last mouthful has been swallowed. It seems that each act of deglutition inhibits the third stage of the preceding one, so that the food slides easily through a relaxed œsophagus.

The cardiac end of the stomach is normally contracted, but relaxes in the last stage of deglutition.

Nervous Mechanism of Deglutition

Deglutition is a complex reflex act, which is started by impulses from the mucous membrane of the fauces or upper part of the larynx. These travel up to the medulla through branches of the fifth nerve and the superior laryngeal branches of the vagus. A movement of deglutition may often be excited by stimulation of the central end of the superior laryngeal nerve.

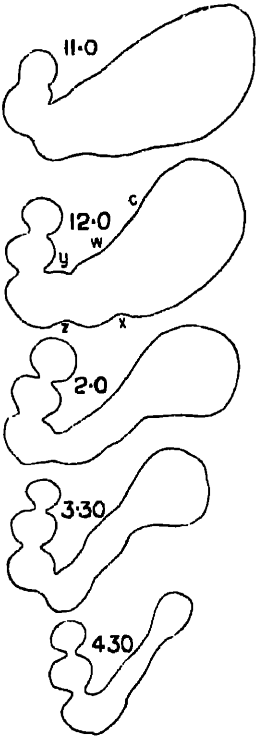
Stimulation of the central end of the glosso-pharyngeal nerve checks any movements of deglutition that are in progress and may excite vomiting.

The efferent channels are the hypoglossal nerve (to the tongue), the fifth (to the mylo-hyoid), the glosso-pharyngeal, vagus, and spinal accessory (to the muscles of the soft palate, pharynx, and œsophagus). The vagus carries both motor and inhibitory fibres for the lower part of the œsophagus and the cardiac sphincter of the stomach. Stimulation of the peripheral end of the vagus in the normal animal causes tonic contraction of the whole œsophagus. If however curare and atropine be given, excitation of the vagus generally inhibits the cardiac sphincter, so allowing of a free flow of fluid from œsophagus to stomach.

Movements of the Stomach

The stomach, which serves at once as a digestive organ and as a reservoir which allows only small amounts of the food at a time to pass into the intestines, is divided into cardiac and pyloric portions. Its muscular coat consists of three layers, an outer longitudinal, a middle circular, and an internal oblique layer, the first being continuous with the longitudinal fibres, and the two latter with the circular fibres of the œsophagus. About the middle of the pyloric half the circular fibres are slightly thickened to form the 'transverse band,' and at the pyloric orifice there is a very pronounced thickening of the same fibres, forming the strong pyloric sphincter. The movements of the stomach in the normal animal have been studied by Cannon, by the administration of subnitrate of bismuth with the food (bread and milk). On examining the animal under the Rontgen rays, the opaque

FIG. 180.



Shadow sketches of the outlines of the stomach of a cat, immediately after a meal (11 0), at various intervals afterwards (12 0, 2 0, 3 30, 4 30), *c*, situation of œsophageal opening, *yz*, 'transverse band,' *wx*, junction of cardiac and pyloric portions (W B Cannon.)

bismuth salt caused a shadow of the outlines of the stomach on the platino-cyanide screen. Figures obtained in this way are shown in Fig. 180. Within five minutes after the end of a meal slight constrictions appear near the middle of the stomach and travel slowly towards the pyloric end. The contractions succeed one another at intervals of ten seconds, so that the pyloric half is occupied with two or three such waves. Ten or fifteen minutes after the first constriction has appeared, the arrival of a wave at the pylorus is attended by a relaxation of the pyloric sphincter and a squirting of some of the contents into the duodenum. After this time the pylorus opens at regular intervals to allow some of the gastric contents to pass. The relaxation of the sphincter is at once inhibited by the arrival of any solid or indigestible particle in the region of the pylorus.

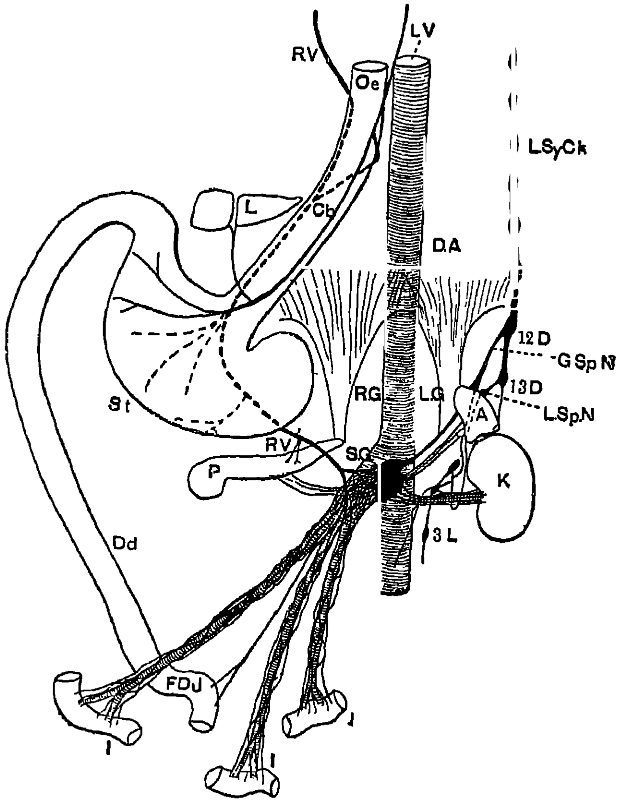
During this time, although free from distinct waves of contraction, the cardiac part of the stomach has not been idle. As the pyloric half empties itself into the duodenum, the cardiac half contracts steadily on its contents, so compelling ever fresh portions of food to enter the pyloric mill. At the end of digestion the cardiac part is contracted to the shape of a tube (Fig. 180, 4.30). The period elapsing from the taking of food to the complete emptying of the stomach may vary, according to the meal taken, from four to sixteen hours.

Nervous Mechanism of the Stomach Movements

The manner in which these co-ordinated muscular contractions are initiated and carried out is quite unknown. Since somewhat similar movements have been observed in the excised stomach, it has been supposed that they are due to a local nervous mechanism; but whether this mechanism is situated in the plexus of Auerbach between the muscular coats, or in the microscopic ganglia which are found at various places under the serous coat, is quite unknown.

From the central nervous system the stomach receives fibres by two ways, viz. from the vagi and from the splanchnic nerves. It is generally stated that the effect of the vagus is to increase, and that of the splanchnic to diminish the stomach movements. It is certain however that the vagi may act either as motor or inhibitory nerves to the walls of the stomach as well as to the cardiac and pyloric sphincters.

FIG. 181.



Distribution of the vagus in the abdomen of the dog (M H. Naylor). *R V*, *L.V* Right and left vagi. The right vagus runs behind the œsophagus (*Oe*) and stomach (*St*), and in those places is represented by a discontinuous line *Cb* Connecting branch between right and left vagi *P* Pancreas *Dd* Duodenum *F.D.J* Flexura duodeno-jejunalis *I*, *I*, *I*, Intestine *L* Liver *K* Kidney *A* Suprarenal capsule. *R G*, *L G* Right and left crura of diaphragm *L.Sy Ch.* Left sympathetic chain. 12 *D*, 13 *D* Twelfth and thirteenth dorsal ganglia 3 *L*. Third lumbar ganglion. *G Sp N.*, *L Sp N* Great and small splanchnic nerves *S G* Left semilunar and superior mesenteric ganglia *D A* Dorsal aorta.

The most usual effect of stimulating the vagus, especially after atropine, is contraction of the pylorus with relaxation of the cardiac sphincter; but in other cases there may be an equally definite contraction of the cardiac sphincter, or an equally definite relaxation of the pyloric sphincter. It is doubtful whether in the higher animals the splanchnics have any direct influence on the muscular wall of the stomach.

Vomiting

Vomiting is a reflex act which lies on the borderland between physiological and pathological processes. It is at any rate the normal reaction of the stomach to an irritant. The act of vomiting is generally preceded by a feeling of nausea, copious salivation, and retching. Retching is a violent inspiration while the glottis is kept firmly closed, so that air is drawn into the œsophagus, and distends it. This stage is followed by contraction of the fibres radiating from the cardiac end of the œsophagus, which opens and allows gas to escape. The head being bent forward and the mouth widely opened, so as to straighten the œsophagus as much as possible, and the glottis kept closed, a forcible contraction of the abdominal muscles occurs, attended by contraction of the muscular wall of the stomach itself, which forces out its contents.

Vomiting can be accomplished by contraction of the stomach alone, or of the abdominal muscles alone; for it may be excited in an animal by injection of apomorphine even after its stomach has been replaced by a bladder, or its abdominal muscles and diaphragm paralysed by section of the intercostal and phrenic nerves. Vomiting may be excited reflexly by irritation of the palate, fauces, stomach, peritoneum, or indeed of any abdominal organ. It may also be excited from the brain, in consequence of emotions or evil smells. The co-ordination of the movements of vomiting is dependent on a centre in the medulla—'vomiting centre'—not far from the respiratory centre. The various emetics may cause vomiting, either reflexly by irritation of the stomach (mustard, salt water, zinc sulphate), or directly by their action on the centre, *e.g* apomorphine.

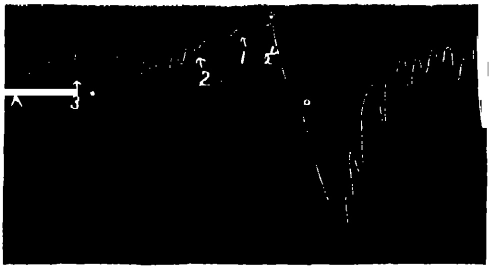
Movements of the Small Intestine

The muscular wall of the small intestine is composed of two continuous layers of longitudinal unstriated fibres externally and circular fibres internally. Between the two layers we find a peculiar nerve-plexus, 'the plexus of Auerbach,' composed of crossing strands of non-medullated nerve-fibres with collections of ganglion cells at their nodal points. Fine fibres given off from this plexus ramify among the muscle-cells on each side. A finer plexus, the plexus of Meissner, lies in the submucosa and sends nerves up into the villi to supply the muscles of the muscularis mucosæ and the glandular epithelium.

On examining the small intestines in a warm saline bath, after division of all nerves connecting them with the central nervous system, they are seen to be in a state of continual movement. The movements are of two kinds. In the first place, all the coils of intestine are in a condition of swaying motion, the movement from side to side being caused by slight waves of constriction affecting both coats simultaneously and travelling rapidly down the intestine at the rate of 2 to 5 cm. per second. They recur at regular intervals of five or six seconds, so that if a rubber balloon be placed in the intestine and connected with a recording tambour, we get a tracing as regular as that of a beating heart. These movements are apparently *myogenic*, *i.e.* they are due to an inherent rhythmicity of the muscle-fibres themselves and are propagated down the intestine from one muscle-fibre to another. They are increased in amplitude by local distension and in frequency by rise of temperature. They are incompetent to push a mass of food onwards, their chief use seems to be to effect a continuous movement and mixing of the intestinal contents. In animals which have been fed with food containing bismuth subnitrate, these contractions may be seen under the Rontgen rays to cause the intestinal contents to break up into segments, which fuse again to be broken up by fresh constrictions. The movements are therefore often called the 'segmenting movements.'

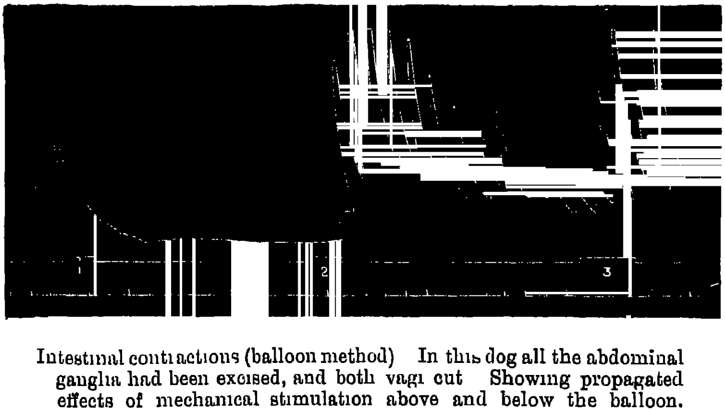
In strong contrast to these segmenting contractions are the true peristaltic waves. Where not present spontaneously in the exposed intestine, they may be easily evoked by introducing a bolus of cotton wool and vaseline into the gut. The introduction of the bolus is at once followed by a twofold effect. Immediately above the bolus, a strong ring of constriction is produced, and this travels slowly down the intestine, driving the bolus before it. The rate of progress of the wave is very variable and may be as little as a centimetre in a minute. The passage of the bolus downwards is rendered possible by an inhibition of all the spontaneous

FIG 182



Passage of bolus Contractions of longitudinal coat (enterograph) The bolus (of soap and cotton wool) was inserted into the intestine four inches above the recorded spot at A The figures below the tracing indicate the distance of the middle of the bolus from the recording levers As the bolus arrived two inches above the levers there is cessation of the rhythmic contractions and inhibition of the tone of the muscle This is followed, as the bolus is forced past, by a strong contraction in the rear of the bolus.

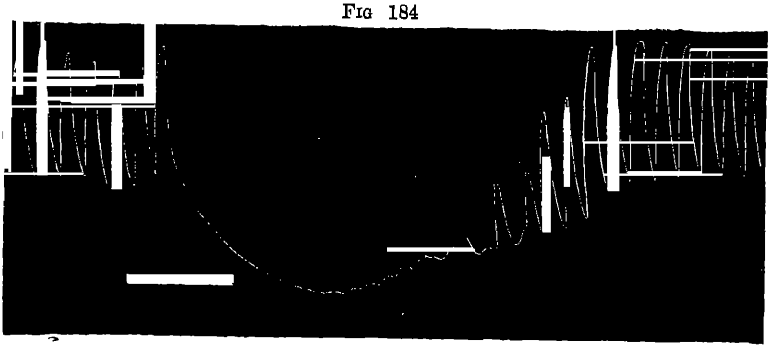
FIG 183



Intestinal contractions (balloon method) In this dog all the abdominal ganglia had been excised, and both vagi cut Showing propagated effects of mechanical stimulation above and below the balloon. (1) pinch above, (2) pinch below, (3) pinch below balloon contractions of the intestinal wall for some distance below the bolus, so that the advancing wave drives the bolus always into a relaxed portion of the gut. A peristaltic wave therefore is a co-ordinated act involving two factors, an excitation above and an inhibition below the excited spot. This twofold effect of local excitation can be easily demonstrated by pinching the intestine above and below a balloon connected with a tambour. A pinch above causes instant relaxation of the gut at the balloon, whereas stimulation just below causes increased tone and increased rhythmic contraction (Fig. 183).

These peristaltic contractions, as well as the double reaction to local stimulus, can be abolished by painting the intestine with cocain or by injection of nicotine. Under these circumstances the rhythmic swaying movements continue as actively as before, but the intestine is powerless to move on a bolus or mass of food. We must therefore regard them as co-ordinated reflexes carried out by the local nervous mechanism—the only example known so far of a true co-ordinated reflex dependent entirely on peripheral nervous structures.

Fig 184

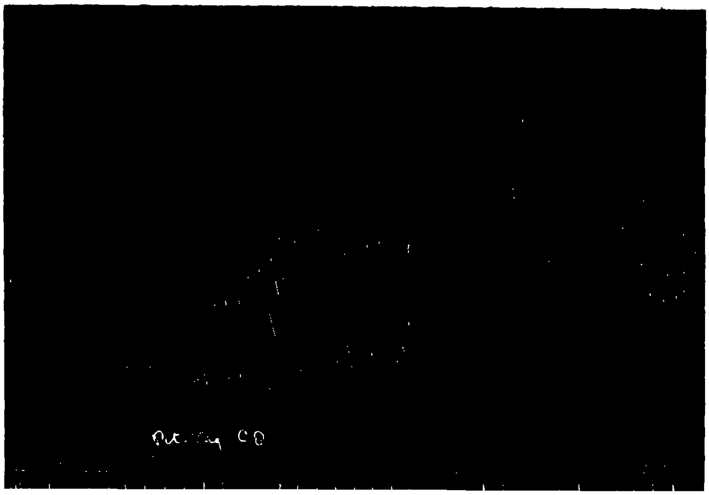


Excitation of both splanchnic nerves Balloon method
Intestine returned to abdomen

Innervation of Small Intestine

The small intestine receives fibres (1) from the greater and smaller splanchnic nerves which run through the semilunar and superior mesenteric ganglia and arrive at their destination along the mesenteric arteries, and (2) from the continuation of the right vagus. The latter however contains fibres from both vagi in the neck. The splanchnic nerves convey purely inhibitory impulses (Fig. 184), the inhibition being independent of the simultaneous effect on the blood-vessels of the intestines. Both longitudinal and circular fibres are involved in the inhibition. Any painful stimulation of a sensory nerve, especially in the abdomen, excites a reflex inhibition, so that it is necessary to cut all the splanchnic fibres if we wish to study by operation the normal activities of the intestine.

Fig. 185.



Effect of stimulation of right vagus on intestinal contractions.

The vagus is a motor nerve to the intestine. Stimulation of the vagus after the administration of atropine (to paralyse the cardio-inhibitory fibres) gives, after a prolonged latent period, increased amplitude of the rhythmic contractions accompanied by augmentation of tone (Fig. 185).

In the dog there is a preliminary temporary inhibition, but this inhibition is possibly determined by an immediate motor effect on the stomach or duodenum, since it is absent in such animals as the rabbit, where a descending inhibition as the result of local stimulation is also absent or little marked.

Movements of Large Intestine

Just as at the upper end of the alimentary canal there is a gradual transition from the co-ordinated cerebro-spinal reflex of deglutition to the local automatic movements of the stomach, so in the large intestine we find a gradual transition in the opposite direction, the activity of the gut becoming less automatic and more dependent on its extrinsic innervation as we proceed from ileo-colic valve to anus. The muscular wall consists, as in the small intestine, of two coats, the outer longitudinal fibres however being especially condensed in man and some animals to form three bands of muscular fibre. The colon separated from its nervous connections shows slow rhythmic contractions, much more irregular and less frequent than those of the small intestine. A peristaltic wave may often be produced in the upper part of the colon or be transmitted onwards from the ileum, but in nearly all cases dies away before arriving at the sigmoid flexure

In the upper part of the large intestine in many animals we find peristaltic movements alternating with antiperistaltic movements, so that the onward movement of the intestinal contents is cut short by a reverse contraction which drives them up against the ileo-cæcal valve. The to and fro movement of the intestinal contents seems specially adapted for enabling the organism to extract the last traces of nutriment from the contents of the gut before these are passed on as fæces into the lower bowel

Innervation of Large Intestine

The colon receives fibres from two sources—from the lower dorsal and upper lumbar nerves, and from the second and third sacral nerves. The upper set of nerves pass by the rami communicantes into the sympathetic chain, thence into the inferior mesenteric ganglion, where many of them make connections with the nerve-cells. From the ganglion they pass as non-medullated nerve-fibres along the branches of the inferior mesenteric artery in the walls of the gut. (Fig. 306.) The sacral fibres pass in the pelvic visceral nerves or nervi erigentes to the hypogastric plexus, whence branches are given off, which run up in the walls of the colon.

The action of these two sets of nerves is exactly analogous to that of the nerves supplying the small intestine, the part of the vagus being taken by the pelvic visceral nerve. The branches of the inferior mesenteric ganglia are purely inhibitory to both longitudinal and circular coats, whereas the sacral nerves cause a strong contraction of both coats, which may in some cases take the form of a descending peristaltic wave, but is in all cases accompanied by a strong contraction of the thickened collection of longitudinal fibres forming the recto-coccygeal muscle. This contraction is in the dog often preceded by a preliminary inhibition analogous to that produced in the small intestine by the vagus.

A well-marked band of circular muscles forms a sphincter at the entry of ileum into colon. It is interesting to note that excitation of the splanchnics, which inhibits all the rest of the gut, causes a strong contraction of the ileo-colic sphincter

Defæcation

The residue of the undigested food and other matters forming the fæces are driven on by the peristaltic contractions of the upper part of the large intestine, until they reach the sigmoid flexure. The mass of fæces accumulates in the sigmoid flexure, and is added to after each meal.

The anus is closed by two distinct muscles—the external sphincter, a thin sheet of striated muscle; and the internal sphincter, a thick ring of unstriated muscle surrounding the last three inches of the rectum, and about half an inch thick. The internal sphincter is normally in a condition of tonic contraction. This contraction however is not usually needed to keep back the fæces, since any that have escaped past the sigmoid flexure are retained in the upper part of the rectum by a transverse fold of mucous membrane. They are also kept back by the acute angle that the last part of the rectum makes with the preceding part, and by the contractions of the perinæal muscles which maintain this curvature and empty the lower part of the bowel.

Defæcation is normally started by a voluntary act, although it may take place involuntarily, as is shown by the fact that it occurs in a dog whose spinal cord has been divided in the dorsal region.

The steps of normal defæcation are as follows:—The glottis being closed, a forcible expiratory effort of the abdominal muscles is made. The perinæal muscles being relaxed at the same time, the lower part of the rectum is straightened, and a portion of the contents of the sigmoid flexure is forced down into the lower part of the rectum. The presence of a foreign body in the lower part of the rectum irritates the mucous membrane, and excites reflexly the rest of the act. Strong peristaltic contractions take place along the whole of the descending colon (sigmoid flexure and rectum), while both sphincters are relaxed, thus forcing out the contents of the bowel. The recto-coccygeal muscle contracts forcibly at the same time, pulling down and straightening the lowest part of the bowel and causing some eversion of the mucous membrane. The last section of the rectum at the close of the act is emptied by a forcible contraction of the levator ani and the other perinæal muscles, and this contraction also serves to restore the everted mucous membrane.

The carrying out of this reflex act is dependent on the integrity of a certain part of the lumbar spinal cord. If this 'centre' be destroyed, the tonic contraction of the sphincter muscles disappears. This centre may be either excited to increased action, or be inhibited by peripheral stimulation of various nerves, or by emotion, such as fear. Application of warmth to the region of the anus causes reflex relaxation of the sphincter; application of cold increases its tonic contraction.

377-423.

CHAPTER IX

RESPIRATION

SECTION 1

THE RESPIRATORY MOVEMENTS

THE processes of external respiration, namely, the taking up of oxygen and the giving off of carbon dioxide—the product of the union of the oxygen with the carbon of the foodstuffs—are effected in the lungs, which are built up in the following way. The trachea or windpipe, a wide tube about 4½ inches long, divides below into two main branches—*bronchi*; and these subdivide again and again, becoming gradually smaller. The terminal ramifications or *bronchioles* open into rather wider parts—the *infundibula*, the walls of which are beset with a number of minute cavities, the *alveoli*. The larger tubes are kept patent by rings or plates of cartilage in their walls. The smaller tubes have no cartilage, their walls being composed of fibrous and elastic tissue and a coating of unstriated muscular fibres, which are able by their contraction to occlude the passage. The whole system of tubes is lined with a layer of epithelium—ciliated columnar in the trachea, bronchi, and bronchioles, and cubical over the parts of the infundibulum not occupied by air-cells.

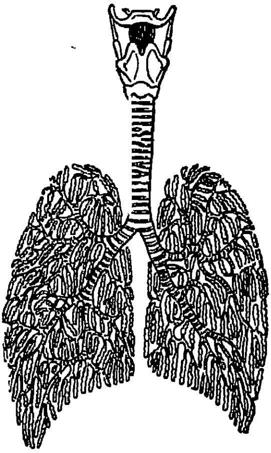
The alveoli are the special respiratory parts of the lung. Their walls are composed of connective tissue containing a large number of elastic fibres, and are covered internally by a single layer of extremely thin large flattened cells. The alveoli are closely packed together, so that in a section of the lung an alveolus is seen to be in contact with others on all sides. Immediately below the squamous epithelium ramify blood-capillaries derived from the pulmonary artery. These form a close network, and the blood in them is in close proximity to air on all sides, being separated from the air in

P241 Letourneaux,

the alveoli only by the thin endothelial cells of the capillary wall and the flattened cells lining the alveoli.

The lungs in their development grow out from the front part of the alimentary canal into the front part of the body-cavity on each side—the pleural cavity. The surrounding body-walls become strengthened by the formation of the ribs, so that the lungs are suspended in a bony cage-work, the thorax. Their outer surface is covered with a special membrane, the *pleura*, which is reflected on to the wall of the thorax from the roots of the lungs, and completely lines the cavity in which they lie. The surface of the pleura facing the pleural cavity is lined with a continuous layer of flattened endothelial cells, and is kept constantly moist by the secretion of lymph into the cavity. Thus, being attached to the thorax only where the bronchi and great vessels enter, the lungs are able to glide easily over the inner surface of the thorax, with which under normal circumstances they are in intimate contact.

Fig 186



Diagrammatic representation of the structure of the lungs The trachea branches into two bronchi, which subdivide again and again before ending in the infundibula (from Yeo).

A constant renewal of the air in the lungs is secured by movements of the thorax, which constitute normal breathing. With inspiration the cavity of the thorax is enlarged, and the lungs swell up to fill the increased space. The capacity of the air-passages of the lungs being thus increased, air is sucked in through the trachea. The movement of inspiration is followed by that of expiration, which causes diminution of the capacity of the thorax and expulsion of air.

The expiration follows immediately upon inspiration. At the end of expiration there is normally a slight pause. The number of respirations in the adult is about 17 or 18 a minute. This is however much influenced by various conditions of the body, and also by the age of the individual. Thus a new-born child breathes about 44 times a minute, a child of five about 26 times, a man of twenty-five about 16, and of fifty about 18. The frequency is increased by any muscular effort, so that even standing up increases the number of respirations. These movements are much affected by psychical activity; they are to a certain extent under the control of the will, although, as we shall see later, they can occur in an animal deprived of its brain, and we know they are normally carried out without any special act of volition. We can breathe fast or slow at pleasure, and can even cease breathing for a time It is impossible however to prolong this respiratory standstill for more than a minute; the need of breathing becomes imperative, and against our will we are forced to breathe.

With every inspiration the cavity of the thorax is enlarged in all dimensions, from above downwards by the contraction of the diaphragm, and in its transverse diameters by the movements of the ribs.

The diaphragm is a sheet of muscle separating the cavity of the chest from that of the abdomen. This sheet, which is tendinous at the centre, is arched, the convex side protruding up into the thorax, forming thus a dome-like boundary of the peritoneal cavity. In expiration the lateral muscular parts of the diaphragm lie in contact with the lower part of the thoracic wall. During inspiration the muscle-fibres contract and draw the central tendon downwards, so that the lower border of the lungs descends (Fig. 188). The enlargement of the lungs at the lower part of the thorax is aided by the abduction of the floating ribs, produced by the contraction of the quadratus lumborum and deep costal muscles. In this contraction the diaphragm presses on the contents of the abdomen, so that the abdomen swells up with each inspiratory movement.

In forced inspiration the descent of the tendinous part of the diaphragm may also involve the heart and inferior vena cava

The enlargement in the other diameters is effected by an elevation of the ribs. Each pair of corresponding ribs, which are articulated behind with the spinal column and in front with the sternum, forms a ring directed obliquely from behind downwards and forwards. With each inspiratory movement the ribs are raised, the obliquity becomes less, and the horizontal distance between sternum and spinal column is therefore increased. Moreover the ribs from the first to the seventh increase in length from above downwards, so that when they are raised, the sixth rib, for instance, occupies the situation previously taken by the fifth, and the transverse diameters of the thorax at this height are increased. With each inspiration there is a rotation of the ribs. In the expiratory condition they are so situated that their outer surfaces are directed not only outwards, but also downwards. As they are raised by the inspiratory movements, they rotate on an axis directed through the fore and hind ends of the rib, so that their outer surfaces are turned directly outwards. In this way a certain enlargement of the thoracic cavity is produced. As the thorax is raised there is always some stretching of the rib cartilages.

Fig 187

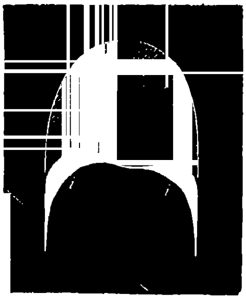


Diagram showing movements of diaphragm in respiration *i i*, inspiratory position; *e e*, expiratory position. (Yeo)

In expiration the processes are reversed, and the cavity of the thorax is diminished in all three dimensions.

The movements of the thorax are effected by means of muscles. Inspiration is performed by the following muscles:

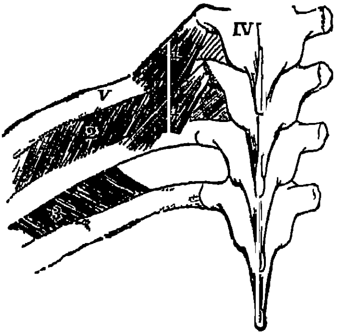
The diaphragm, which is the most important, and almost suffices alone to carry out quiet respiration.

The external intercostal muscles, which shorten and so raise the ribs.

The levatores costarum and serratus posticus superior.

These muscles are the only ones normally engaged in carrying out inspiration. When, in consequence of muscular exertions or from any other cause, the inspiratory efforts become more forcible, a large number of accessory muscles are brought into play. These are—

Fig 188



Four dorsal vertebræ and their ribs to show attachments of respiratory muscles (A. Thomson) 1 1, levatores costarum, 2, external intercostal; 3, internal intercostal.

The scaleni,
Sterno-mastoid,
Trapezius,
Pectoral muscles,
Rhomboids, and
The serratus anticus

Normal expiration is chiefly effected passively. When the inspiratory muscles cease to contract, the lungs, which were stretched by the previous inspiration, contract by virtue of the elastic tissue they contain, and the thorax itself sinks by its own weight, and by the elastic reaction of the stretched costal cartilages. Probably under normal circumstances the internal intercostal muscles also contract with each expiration.

Although the action of the intercostal muscles has been a subject of debate, physiological experiments serve on the whole to confirm the view first put forward by Hamberger and based on a consideration of the direction of the fibres. The external intercostals pass from one rib to the next below downwards and forwards Hence if a pair of ribs be isolated from the rest of the chest-wall, leaving the vertebral and costal attachments intact, contraction of these muscles will cause a rise of both ribs. This result will be evident from a consideration of Fig 189, where *a b* is a fibre of the external intercostal muscles, passing from the rib *v s* to be attached to the rib *v′ s′* at *b* When *a b* contracts, the tension it exerts on its two attachments can be resolved into two components *a c* acting downwards and *b d* acting upwards *b d* however acts at the end of the long lever *b v′*, whereas *a c* acts at the end of a short lever *a v*. Hence the raising effect will overcome the depressing effect, and both ribs will rise

Fig 189

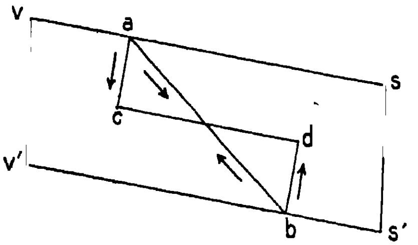
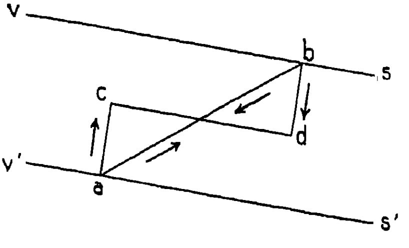


Fig 190



The fibres of the internal intercostals run in the opposite direction to the external muscles, and from a consideration of Fig 190 it is evident that their effect will be to depress any pair of ribs, thus acting as expiratory muscles

Owing to the fact that the costal cartilages make an angle with the bony ribs, the fibres of prolongation of the internal intercostals, *musculi intercartilaginei*, have the same relation to their attachments that the external intercostals have to the bony ribs Their action therefore must be to raise the cartilages and flatten out the angle between the cartilaginous and bony ribs, so that they must act with the external intercostals as inspiratory muscles

In forced expiration a large number of muscles may take part—such as the serratus posticus inferior, and the muscles forming the wall of the abdomen, *i.e.* the rectus, obliquus, and transversus abdominis muscles.

As the lungs expand with each inspiration, their position changes somewhat in relation to the thoracic wall. The roots, the hinder borders, and the apices of the lungs remain nearly stationary. The front parts move downwards and inwards, so that their inner borders in front approach one another. By percussing the chest, it may be easily made out that the resonant area, corresponding to the parts where the lungs are in contact with the thoracic walls, increases with each inspiration, and diminishes with each expiration.

Even at the end of expiration the lungs are in a stretched condition. This is shown by the fact that if in an animal or in the corpse an opening be made into the pleural cavity, air rushes into the opening and the lungs collapse, driving a certain amount of air out through the trachea. Since then the lungs are always tending to collapse, it is evident that they must exert a pull on the thoracic wall This pull of the lungs gives rise to a *negative pressure* in the pleural cavity. If we connect a mercurial manometer with the pleural cavity, we find this pull of the lungs amounts in the corpse to 6 mm. of mercury. If the lungs are fully distended, as after full inspiration, the elastic forces are more brought into play, and the negative pressure in the pleura may amount to 30 mm. Since the lungs are always tending to collapse, respiration becomes impossible directly free openings are made into the pleural cavities on both sides. With each inspiratory movement air rushes in through these openings, so that the thoracic movements can no longer exert any influence on the volume of the lungs. The negative pressure in the thorax is diminished by any factor decreasing the elasticity of the lung-tissue. Thus in an old man, where the elastic tissue is degenerated and the alveoli are enlarged, giving rise to the condition known as emphysema, the lungs may collapse only slightly or not at all on opening the chest. The lungs do not collapse on making an opening in the chest of a new-born mammal; but this is owing to the fact that the lungs completely fill the thorax in the expiratory position, and it is only later that with the growth of the ribs the thorax gets, so to speak, too large for the lungs, which are therefore stretched to fill it.

The force exerted by the inspiratory muscles is nearly all spent in overcoming the elastic resistance of the lungs and costal cartilages. A free access of air is provided for by contractions of certain accessory muscles of respiration With each inspiration the glottis is widened by abduction of the vocal cords. When the glottis is observed by means of the laryngoscope, a rhythmical separation and approximation of the vocal cords are observed, synchronous respectively with inspiration and expiration. When inspiration is laboured, the alæ nasi are dilated by the action of the dilatator nasi. This movement of the nostril, which is constant in many animals, becomes very prominent in children suffering from any respiratory trouble.

If a manometer be connected with one of the nostrils, so as to register the pressure in the air-cavities, it is found that there is a negative pressure of − 1 mm. Hg with inspiration, and a positive pressure of 2 or 3 mm. with expiration. With forced inspiration the negative pressure may amount to −57 mm. Hg, and with forced expiration there may be a positive pressure of + 87 mm.

Under no circumstances can we by forced expiration empty the lungs of air. At the end of the most forcible expiration, if the pleura were perforated, the lungs would collapse and drive more air through the trachea. When breathing quietly a man takes in and gives out at each breath about 500 c.c. of air, measured dry and at 0° C. If measured moist and at the temperature of the body, viz. 37° C, the volume would be 604 c.c. This amount is known as the *tidal air*. By means of a forcible inspiratory effort it is possible to take in about 1,500 c.c. more (*complemental air*). At the end of a normal expiration a forcible contraction of the expiratory muscles will drive out about 1,500 c.c. more (*supplemental air*). These three amounts together constitute the 'vital capacity' of an individual This total may be determined by means of the instrument known as the spirometer, which is merely a small gas-meter with a gauge by which the amount of air in it can be at once read off. The person to be tested fills his lungs as full as possible, and then expires to the utmost into the spirometer. The air left in the lungs after the most vigorous expiration (*residual air*) amounts to about 2,000 c.c.

The residual air may be determined by letting a person expire to the utmost extent and then connecting with his mouth or nose a bag of known capacity filled with hydrogen. The subject of the experiment then inspires and expires into the bag two or three times, ending in the same state of forced expiration as he began. Any diminution of the total volume of gas in the bag will represent the gas lost during the experiment by diffusion into the blood-vessels. By analysis of the gaseous mixture in the bag, it is possible to determine the amount of air in the lungs at the beginning of the experiment. Supposing for example the bag held 4,000 c.c. hydrogen, after two respirations the total volume is unaltered, but the gas is found to consist of 3,000 c.c. hydrogen and 1,000 c.c. oxygen, nitrogen, and CO_2, *i.e.* pulmonary gases. Since the gas in the lungs must have the same composition and 1,000 c.c. hydrogen have disappeared from the bag, it is evident that the lungs will contain 1,000 c.c. hydrogen and $\frac{1000}{3}$, *i.e.* 330 c.c. pulmonary gases. Thus the total volume of gas left in the lungs at the end of the forced expiration was 1,330 c.c., which is the residual volume for the individual.

Of the 500 c.c. of tidal air taken in at each inspiration, only a certain part reaches the alveoli, part being required to fill the air-tubes, trachea, bronchi, and bronchioles which lead to the air-cells. The volume of the air-tubes has been reckoned to amount to 140 c.c., so that of the 500 c.c. about 360 c.c. reach the alveoli. For the same reason the expired air represents the air from the alveoli (360 c.c.) diluted with 140 c.c. of air which has remained in the air-tubes and undergone very little change, other than the elevation of temperature and saturation with aqueous vapour. We have therefore to allow for this air contained in the so-called 'dead space' of the lungs when we seek to arrive at the composition of alveolar air from an analysis of expired air. We must remember however that the air in this dead space is not absolutely wasted, since it is constantly undergoing interchange by diffusion with the alveolar air, and thus serves to carry some of the oxygen to and some of the CO_2 away from the pulmonary alveoli, although never in contact with the latter.

SECTION 2

CHEMISTRY OF RESPIRATION

The respiratory movements are but means to an end. They enable the blood to take up oxygen and give off carbon dioxide on its way through the lungs, so that the blood reaches the tissue-elements prepared to supply them with oxygen and to take up carbon dioxide, the product of their destructive metabolism. We have now to study the conditions that regulate gaseous interchange in the lungs and in the tissues.

As we should expect, analysis shows marked differences in the constitution of inspired and expired air. Inspired air—that is to say, ordinary atmospheric air—consists of a mixture of oxygen and nitrogen, with a very small trace of carbon dioxide gas. Its composition is—

Oxygen .	20·96 vols.	per cent
Nitrogen .	79 „	„
Carbon dioxide .	0·04 vol.	„

It also contains a variable amount of watery vapour, but is very rarely saturated with it. Its temperature of course varies with the season of the year.

The chief change that occurs in respired air is a decrease of the oxygen, and a corresponding increase of carbon dioxide. Its average composition in man is—

Oxygen . .	16·0 vols.	per cent
Nitrogen .	79·6 „	„
Carbon dioxide	4·4 „	„

It is moreover nearly saturated with watery vapour, which on a cold day condenses in a cloud of steam with every expiration. Its temperature, which is very slightly affected by that of the external air, is a little below the normal body temperature (about 36° C.). If the inspired air is above the body temperature, the expired air is found to be cooled down to the temperature of the body. If the inspired and expired air be carefully measured in a dry condition at the same temperature, it will be found that the volume of expired air is about $\frac{1}{50}$ less than that of the inspired. The conversion of oxygen into carbon dioxide would not of course cause any change in the volume of the gas; for one molecule of oxygen (O_2)

Combined with Gr [illegible]

would, on combining with carbon, give rise to one molecule of carbon dioxide (CO_2), which at the same temperature and pressure would occupy exactly the same volume. But it must be remembered that carbon is not the only element which leaves the body in an oxidised condition. Fats, for example, contain a number of unoxidised atoms of hydrogen, which in the metabolic processes of the body are fully oxidised to be excreted as water. A certain amount of oxygen too is used up in the oxidation of the nitrogenous elements of food, which are excreted chiefly as urea. Thus a certain amount of oxygen is taken in, which does not reappear as CO_2 in expired air. Hence, although the total volume of nitrogen expired is the same as that inspired, its *percentage amount* is rather greater in expired than in inspired air. We should expect to find this apparent loss of oxygen greater in carnivora, whose food consists mainly of proteins and fats, than in herbivora, which feed principally on carbohydrates. This indeed is found to be the case.

The quotient $\frac{CO_2 \text{ expired}}{O_2 \text{ inspired}}$ is known as the *respiratory quotient*. From the preceding remarks, it is evident that it can never be greater than 1, if the observation be extended over a fairly long period, and that it is less in carnivora than in herbivora.

If an animal could live on a purely carbohydrate diet, its respiratory quotient would be exactly 1, since the hydrogen and oxygen in the carbohydrate molecule are in the exact proportion to form water and can therefore be disregarded Thus

$$\underset{\text{(Dextrose)}}{C_6H_{12}O_6} + 6\,O_2 = 6\,CO_2 + 6\,H_2O$$

The case is different with fats. If we assume an animal to be fed on pure olein, the respiratory changes will be represented as follows:

$$C_3H_5(C_{18}H_{33}O_2)_3 + 80\,O_2 = 57\,CO_2 + 52\,H_2O.$$

Here the respiratory quotient is $\frac{57}{80} = 0{\cdot}71$

Egg albumen may be roughly represented as $C_{102}H_{160}N_{26}O_{33}S$ The oxidation would take place as follows.

$$C_{102}H_{160}N_{26}O_{33}S + 107\tfrac{1}{2}\,O_2 = 89\,CO_2 + 54\,H_2O + 13\,\underset{\text{(Urea)}}{CON_2H_4} + SO_3.$$

Here the respiratory quotient is $\frac{89}{107{\cdot}5} = 0{\cdot}82.$

In the case of the isolated frog's muscle, or of the whole frog in an atmosphere of nitrogen, the respiratory quotient may be very large. In warm-blooded animals however, the intake of oxygen must always run parallel to the output of CO_2, and it is not found that moderate muscular activity alters in any way the respiratory quotient. With very severe exercise leading to dyspnœa, there may be a temporary rise of the quotient, but such a condition cannot be regarded as normal.

On the other hand very considerable alterations may take place in the respiratory quotient, if the organism is, so to speak, altering its invested capital, and converting a large amount of carbohydrates into fat, or fat into carbohydrates. This will be evident if we compare the formula for a fatty acid with that of dextrose. Thus:

$$C_{18}H_{36}O_2 + 8\ O_2 = 3(C_6H_{12}O_6$$

Thus to convert fat into carbohydrate, a large amount of oxygen must be taken in, which will not appear at all in the excreta. The respiratory quotient $\frac{CO_2}{O_2}$ will be therefore very small, and in hibernating animals, where this change occurs to a large extent, it may not exceed 0·2 or 0·3; and the animal may even gain weight by the absorption of oxygen. On the other hand when carbohydrates are being largely converted into and stored up as fat, a large amount of oxygen will be available for the production of CO_2 from the simple decomposition of the carbohydrate. In such cases $\frac{CO_2}{O_2}$ will be large, and may amount to as much as 1·5.

As was shown on p. 385, only a certain percentage of the 500 c.c. of tidal air reaches the alveoli, 100 to 140 c.c. being required to fill the trachea and bronchial tubes. Hence the alveolar air must contain more carbon dioxide and less oxygen than the tracheal air; and it is found that, if we take the air from the alveoli instead of that expired through the mouth or nose, the differences between it and the inspired air are much more pronounced.

A sample of alveolar air may be obtained for analysis in the following way (Haldane). A piece of indiarubber tubing is taken of about 1 inch diameter and 4 feet long Into one end (Fig 190A) is fitted a mouthpiece, the other being left open or connected with a spirometer About 2 inches from the mouthpiece is fixed a gas sampling-bulb, which is provided with three-way taps at the upper and lower ends. Before an experiment the bulb is filled with mercury, if the lower end is open, or else it is completely exhausted The subject of the experiment, after breathing normally a few times through the tube, at the end of a normal inspiration, expires quickly and deeply and closes the mouthpiece with his tongue. The tap of the sampling-bulb is then turned, and the air last expelled from the lungs (which is therefore pure alveolar air) rushes into the bulb The top of the bulb is then turned off, and the gas may

FIG 190A.

be removed for analysis. A similar sample is then taken, in which the subject expires deeply at the end of a normal expiration. This sample will, of course, contain more CO_2 and less O_2 than that obtained at the end of inspiration The mean of the two samples is taken as the average composition of alveolar air

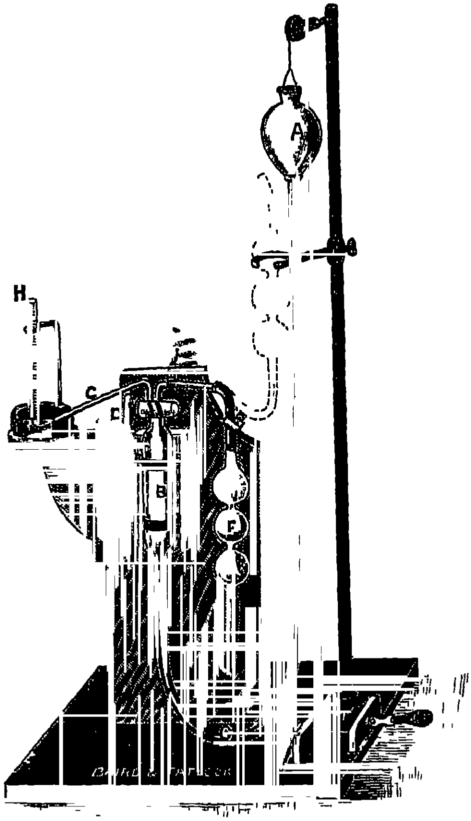
The difference between the composition of expired air and alveolar air is determined by the dilution of the alveolar air with that contained in the dead space. Hence with shallow breathing there will be a large difference, but this will decrease with increased depth of respiration. Thus if the alveolar air contained 6 per cent. CO_2 and the dead space amounted to 150 c.c., the expired air would only contain 3 per cent. CO_2 when the person was taking in only 300 c.c. at each respiration. If however he was breathing slowly and deeply so as to raise the tidal air to 1,500 c.c , only one-tenth of this would be represented by the dead space, and the expired air would contain nine-tenths as much CO_2 as the alveolar air, *i.e.* 5·4 per cent

Respiratory Changes in the Blood

From 100 volumes of either venous or arterial blood we can, by means of the mercurial pump, remove about sixty volumes of gas.

A great variety of pumps has been devised for this purpose. One of the simplest of these (Hill's blood-pump) is shown in Fig 191, and will serve to illustrate the principle on which all the other pumps are constructed. 'In extracting the gases of the blood by means of this pump, a blood receiver is affixed to the end of the tube E, and the receiver is elevated into the position indicated by the dotted outline The receiver (B) is then put in connection with the tube (E) by means of the three-way tap (D), the reservoir (A) is raised above the pump, and the whole system is filled with mercury to the top of the blood receiver (F). The screw clip on the rubber tube, at the upper end of F, is then closed, and the reservoir (A) lowered until the blood receiver is exhausted, except for 2 or 3 c c of mercury, which are purposely left within The screw clip on the lower end of F is next closed, and the blood receiver now clipped at either end, exhausted, detached from tube E, and weighed A sample of blood is then collected in the following way —The arterial or venous cannula is filled with blood, and immediately afterwards pushed into the rubber tube at the end of

FIG 191.



Blood gas-pump of L Hill. This consists of a mercury reservoir (A) about 300 c c. in capacity, which is connected with a second reservoir (D) by means of 120 c m. of pressure tubing The upper end of the reservoir (B) is closed by a three-way tap (D). By means of this tap the reservoir (B) can be put in connection with either the tube (E) leading to the blood receiver (F), or with the tube (C) leading to the eudiometer (H) The tubes E and C are made of manometer tubing The blood receiver (F), which also acts as the froth chamber, consists of three glass bulbs connected by short and wide junctions To either end of the blood receiver is fixed a piece of pressure tubing, provided with a screw clip

the blood receiver, as far as the closed screw clip Before the insertion of the cannula, the end of the rubber tube is compressed with the fingers to exclude the air within it A sufficient quantity of blood is now withdrawn by opening at the same time the screw clip, and the clip placed on the vessel of the animal

The blood is defibrinated by shaking it with the mercury left within the blood receiver for that purpose, and the latter is then again weighed. The weight of the sample of blood is then obtained. The blood receiver is once more affixed to the tube (E), in the dependent position shown in the figure, and the tube (E) is exhausted. Finally, the screw clip between E and the blood receiver is opened, and the gases are withdrawn and collected in the eudiometer. Since the blood receiver hangs freely from the tube (E) by means of a piece of rubber tubing, it can be both immersed in warm water, and shaken to facilitate the complete escape of the gases The bulbous form of the blood receiver prevents the blood from frothing over into the pump, and if the action becomes too violent, it can be immediately allayed by pouring a few drops of warm water on to the tube (E) The bubbles are thereby driven back into the receiver, and the pump is never fouled The tap (D) is so manipulated that the gases only, and not the water which condenses in the reservoir (B), are driven over into the eudiometer The water is turned back into the blood receiver Three to four exhaustions are sufficient to extract all the gases from about ten grammes of blood The gases are estimated by the potash and pyrogallic acid method '

The composition of this gas varies considerably in venous, but not so much in arterial blood.'

The average composition of the gases of dog's blood is given in the following table:

From 100 vols	May be obtained		
	Of oxygen	Of carbon dioxide	Of nitrogen
Of arterial blood	. 20 vols.	40 vols.	. 1 to 2 vols.
Of venous blood	8 to 12 vols.	. 46 „	. „ „

Measured at 760 mm and 0° C.

Thus the analyses of expired air and of the gases of the blood show clearly that the latter, in its passage through the lungs, takes up oxygen and gives off carbon dioxide. In the tissues the reverse process occurs, so that the venous blood returns to the lungs deprived of a portion of its oxygen, and loaded with CO_2. In studying the mechanism of this gaseous interchange, it will be convenient to treat the two gases separately, since their behaviour in the blood and tissues seems to be largely independent of each other.

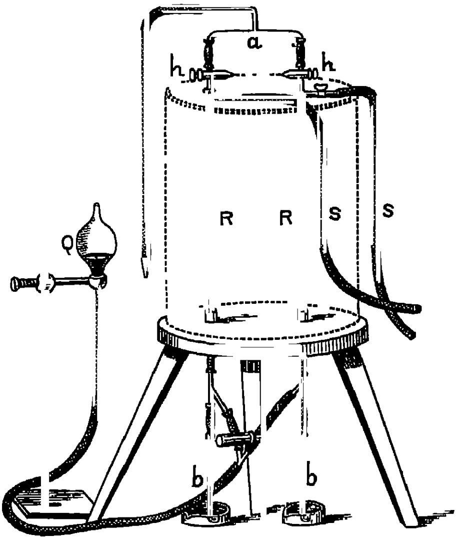
The oxygen in the blood is nearly entirely carried by the hæmoglobin of the red blood-corpuscles. The serum or plasma of the blood cannot take up more oxygen than the same bulk of water—less than 1 per cent. at the ordinary atmospheric pressure and temperature. On the other hand, if from a given specimen of blood we extract the hæmoglobin and dissolve this in water, we find that the pure hæmoglobin is able to absorb as much oxygen as the original blood on being exposed to or shaken with pure oxygen or air, What is the condition of the oxygen in the blood? Is it simply dissolved, or does it enter into chemical combination with the hæmoglobin?

It is well known that, when a gas is dissolved by a liquid, the amount of gas taken up by the liquid varies directly as the pressure of the gas. Thus if one hundred volumes of water at 0° C. would dissolve four volumes of oxygen at a pressure of one atmosphere, it would dissolve eight volumes at a pressure of two atmospheres. At a pressure of three atmospheres the amount dissolved would be twelve volumes. If the liquid be removed from an atmosphere of oxygen at a pressure of two atmospheres to an atmosphere at a pressure of one, oxygen will be given off by the water until equilibrium is established between it and the surrounding medium; the water will then contain only four volumes per cent. At a pressure of half an atmosphere the amount dissolved will be two volumes. In this case it makes no difference to the amount of oxygen dissolved, whether the oxygen is alone or whether it be mixed with some other gas. Thus the amount dissolved will be the same, whether the water be exposed to pure oxygen at a pressure of 380 mm. Hg, or to a mixture of equal volumes of oxygen and nitrogen at a pressure of 760 mm. Hg. In each case the *partial pressure* or *tension* of the oxygen is the same, and therefore the same amount is dissolved.

When equilibrium is established between a gas and a liquid, so that no gas is being taken up or given off by the liquid, the tension of the gas dissolved in the fluid is equal to that in the gaseous medium. On this fact is based the method of determining the tension of a gas dissolved in liquid. The liquid is brought into contact with gaseous mixtures containing various proportions of the gas in question. It is found that the liquid gives off gas to some of these mixtures, and from others takes up gas. By making various experiments a gaseous mixture will be found with which the liquid is in equilibrium. If we know beforehand the amount of gas in this gaseous mixture, we know its tension and therefore the tension of the gas in the liquid.

Pflüger's aërotonometer (Fig 192) consists of two glass tubes, R and R, contained in a vessel filled with water at the temperature of the body. The upper ends of the tubes are connected by the tube *a* with the artery or vein in which it is desired to estimate the tension of the blood gases. If for instance we wish to determine the tension of CO_2 in venous blood, where we expect the tension to amount to about 4 per cent of an atmosphere, one tube R is filled with a gaseous mixture containing 3 per cent CO_2, and the other tube R with a mixture containing 5 per cent CO_2. *a* is now connected with the distal end of the jugular vein, or with the central end of the carotid artery, and blood is

FIG. 192



Pflüger's aërotonometer

allowed to flow and pass in a thin stream down the walls of the tubes R and R, thus presenting a large surface to the contained gases. The blood collects in the lower narrower portions of the tubes, and runs out into the vessels *b*, *b*, whence after defibrination it is returned at intervals into the veins of the animal. Details of an experiment of this description carried out by Frédéricq, using however a single instead of a double tube, will serve to illustrate the method employed.

Determination of Tension of Gases in Arterial Blood

Dog, 12 kilos. Received injection of 'peptone' at 2.15 p.m.

Time	Percentage composition of gas in aerotonometer		Probable value of O_2 and CO_2 tensions (in percentage of an atmosphere)
	At beginning	At end	
2.34—3.34	$CO_2 = 5.07$ $O_2 = 10.8$	$CO_2 = 2.106$ $O_2 = 13.01$	$O_2 = 13$ to 14.8 per cent $CO_2 = 2.41$ per cent
3.36—4.36	$CO_2 = 0.53$ $O_2 = 15.175$	$CO_2 = 2.72$ $O_2 = 14.83$	

In this experiment the CO_2 tension of the blood was lowered in consequence of the injection of albumoses.

One grm. of crystallised hæmoglobin can absorb about 1·4 c.c. of oxygen. If a solution of this oxyhæmoglobin be subjected in an air-pump to gradually diminishing pressure at the temperature of the body, it will be found that very little oxygen is given off until the partial pressure of the oxygen is diminished to about 30 mm. Hg. At this point a large evolution of gas begins, and continues at falling pressure until at 0 mm. pressure all the oxyhæmoglobin is dissociated and converted into hæmoglobin. The same observation may be made in a reverse direction. If a solution of reduced hæmoglobin be exposed to gradually increasing pressures of oxygen, it will be found that the greatest absorption takes place between 0 and 30 mm. Hg. After this point the oxygen is very slowly absorbed, and the further absorption goes on in proportion to the partial pressure of oxygen.

The following table gives the relative proportions of hæmoglobin and oxyhæmoglobin in a blood containing 13 per cent hæmoglobin and exposed to air at various pressures at a temperature of 37·4° C (Hüfner).

Atmospheric pressure in mm. Hg	Partial pressure of Oxygen in mm Hg	Hæmoglobin percentage	Oxyhæmoglobin percentage
760	160	5 4	94 6
524 8	110	7 6	92 4
357 8	75	10 8	89 2
238 5	50	15·4	84 6
119 3	25	26 7	73 3
47 7	10	47 6	52 4
23 8	5	63 9	36 1
0 0	0 0	100 00	0 00

In the curve in Fig 193 the divisions along the base line correspond to the partial pressure of the oxygen in mm Hg, and those along the upright lines (the ordinates) to percentage of saturation of the hæmoglobin with oxygen.

In the case of simple solution, the relation between the pressure of a gas and the amount absorbed would be represented by a straight line

Since there is no direct proportion between the partial pressure of the oxygen and the amount absorbed, it is evident that the oxygen combines with hæmoglobin to form an unstable chemical compound, and that this is not a mere question of solution. This is further proved by the fact that we can displace the oxygen (O_2) from the oxyhæmoglobin by equivalent amounts (*i.e.* by equal volumes) of CO or NO.

A knowledge of these facts makes it easy to understand how the oxygen is taken up by the blood as it circulates round the pulmonary alveoli. Arterial blood, such as that which fills the pulmonary veins and the systemic arteries, is very nearly saturated with oxygen, and will only take up about 1 per cent. more on shaking it with air at the body temperature. Venous blood requires 8 to 10 volumes per cent. of oxygen to saturate it; but we have already mentioned that, at a tension of 30 mm. oxygen, the blood becomes more than three-quarters saturated. The tension of oxygen in the alveoli is considerably above this. In the trachea the tension of oxygen is about $\frac{1}{6}$ of an atmosphere (since the air here contains 16 volumes per cent.), and the tension in the alveoli will be only a little lower than this. If we take the oxygen tension in the alveoli at $\frac{1}{7}$ of an atmosphere,[1] it will still be something over 100 mm. Hence the venous blood brought to the alveoli by the pulmonary artery will, on there coming into intimate contact with the atmosphere, take up oxygen from it to saturation, or to a point not far removed from it.

FIG. 193.

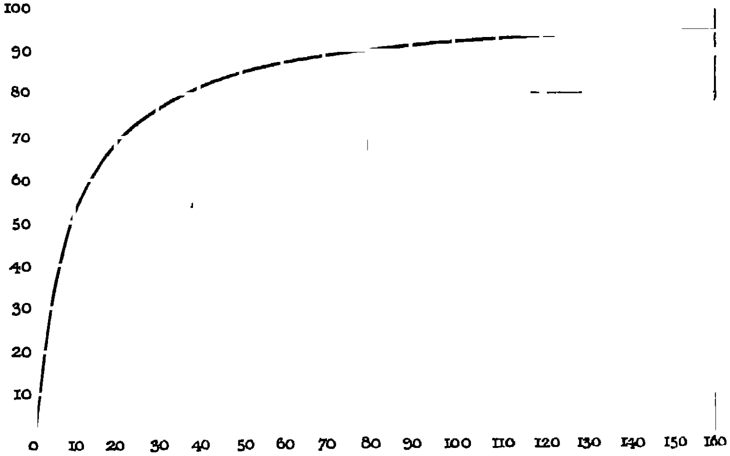


Diagram from Hüfner, to show the percentage saturation of hæmoglobin with oxygen at different pressures of the gas

The blood, thus laden with oxygen, travels to the left side of the heart, and from there is sent through the arteries to all parts of the body. It must be remembered that neither in the lungs nor in the tissues does the hæmoglobin come in actual contact with the source of the oxygen, nor with the cells which it is to supply. In both cases the interchange is effected through the intermediation of the plasma and, in the tissues, of the lymph as well. Since the tissue-elements are constantly using up oxygen, which they build up into their living protoplasm, they absorb any oxygen that is present in the surrounding lymph. There is, in consequence, a descending scale of oxygen tensions from red blood-corpuscle through plasma, vessel-wall, lymph, and tissue-element. The cell draws from the lymph, the lymph from the plasma, so that the oxygen tension in the plasma sinks. This has the same effect as if we put the red corpuscles in a mercurial pump and lowered the pressure of gas. The immediate result is an evolution of oxygen, which is taken up by the plasma, to be in turn passed on to the lymph and the tissue-cell.

---

[1] The oxygen tension in the alveoli has been reckoned at about 12.6 per cent. to 13.5 per cent. of an atmosphere.

Under normal circumstances a blood-corpuscle never stays long enough in the proximity of the tissues to lose its whole store of oxygen. If however the further supply of oxygen to the blood be prevented, as in asphyxia, the last traces of oxygen disappear from the blood. The enormous avidity of the tissues for oxygen is shown by the following experiment (Ehrlich). If a saturated solution of methylene blue be injected into the circulation of a living animal and the animal be killed ten minutes later, it is found on first opening the body that most of the organs present their natural colour, although the blood is a dark-blue colour. On exposure to the atmosphere all the organs acquire a vivid blue colour. The avidity of the tissues for oxygen has been so great that they have been able to decompose the methylene blue molecule, with the formation of a colourless reduction-product, which on exposure to the air undergoes oxydation again and reforms methylene blue. If then the tissues are able to effect the reduction of a comparatively stable body like methylene blue, it is easy to understand their power of reducing oxyhæmoglobin, which is so unstable that it is decomposed by simple physical means such as exposure to a vacuum.

It was long debated whether the chief processes of oxidation took place in the blood or in the tissues. Our experiences with muscle would alone serve to convince us that in some tissues, at any rate, processes of oxidation take place, and the methylene blue experiment shows that these processes of oxidation are intense in all the chief organs of the body. It has been found moreover that it is possible to keep a frog alive after substituting normal saline solution for his blood, if he be placed in absolutely pure oxygen, and that in this case indeed the metabolism of the animal goes on as actively as before. As the frog has no blood, it is evident that its metabolic processes, consisting of the taking up of oxygen and the giving out of carbon dioxide, must have their seat in the tissues.

The relations of carbon dioxide in the blood and the manner of its excretion through the lungs are rather more complicated and obscure than in the case of oxygen. If a given volume of blood be divided into plasma or serum and corpuscles, it will be found that the larger proportion of the carbon dioxide in the whole blood is contained in the serum, although a certain amount is also present in the corpuscles. When extracting gases from serum by means of the mercurial pump, it is found that about 5 per cent. of the carbon dioxide present is fixed[1]—that is to say, is only liberated after the addition of some weak acid, such as phosphoric or tartaric acid. If however we use whole blood for the experiment, it is found that the entire amount of CO_2 is given off. This is shown by the fact that, after extracting with the pump as much CO_2 as possible, no further amount can be obtained on addition of phosphoric acid. Hence the red corpuscles act the part of a weak acid, and we can, in fact, in the first experiment use fresh red corpuscles instead of phosphoric acid to drive off the last trace of CO_2.

From 100 volumes of venous blood we can extract about 50 volumes of CO_2. The question now arises: Is this gas in a condition of solution or in chemical combination with the plasma? The answer is easy to give. At the temperature of the body 100 volumes of plasma would take up 50 volumes of CO_2 at 760 mm. Hg pressure, *i.e.* if we may consider the solubility of the gas in plasma equal to its solubility in water. If therefore CO_2 exists in a state of solution in the plasma, its tension will be 760 mm. Hg, that is to say, one atmosphere. Now the CO_2 tension in venous blood may be determined by the method indicated later (p. 417), and is found to be equal to only 5 per cent. of an atmosphere. This merely means that when the venous blood is brought into an atmosphere containing 5 per cent. CO_2, the relative proportions of CO_2 in the liquid and the gas remain the same. We see then that only $\frac{1}{20}$ part of 50 volumes can be absorbed, since the CO_2 tension is only $\frac{1}{20}$ of an atmosphere; and must conclude that of the 50 volumes $\frac{50}{20} = 2\frac{1}{2}$ volumes are in simple solution, and the remaining $47\frac{1}{2}$ volumes in chemical combination.

---

[1] It must not be thought that these 5 volumes per cent represent the whole of the CO_2 that is chemically combined. The fact that a part of the gas is given off on exposure to a vacuum, and a part left in solution, shows merely either that one part is in a state of looser chemical combination than the other, or that the phosphates in the serum only suffice to take up part of the soda liberated by the decomposition of the sodium carbonate.

On analysing the ash of the serum, we find that it contains sufficient sodium present to combine with all the CO_2, besides that which is necessary to satisfy the fixed acids, hydrochloric and phosphoric. The presence of phosphates as well as proteins (which may act as weak acids) in the serum is probably of great importance for the regulation of the tension of the CO_2. If the two acids, carbonic and phosphoric, are present together in a solution containing soda, the salts formed depend on the relative masses of the two acids. If the carbonic acid is in excess, sodium carbonate is formed, together with monosodium phosphate (NaH_2PO_4). If however the carbonic acid be removed, or its 'mass influence' diminished by allowing it to escape freely into a vacuum, the phosphoric acid gains the upper hand and takes the lion's share of the sodium, disodium phosphate (Na_2HPO_4) being formed. In this way, as soon as the amount of free carbon dioxide decreases, however little, the amount of the CO_2 in combination also diminishes, and moreover to a very considerable extent. Thus in the serum, where these two salts are present, an alteration of eight volumes per cent. in its CO_2 gives rise to a change of tension of only 2·6 per cent. of an atmosphere.

In other words a distinct advantage is gained if the CO_2 in the plasma is, like the oxygen in the corpuscles, in a condition of unstable chemical combination A rise of oxygen tension from 0 to 25 mm. gives a rise of oxygen carried from 0 vols, per cent to 15 vols per cent (taking 20 vols per cent. as maximum saturation of the hæmoglobin), while a rise of CO_2 tension from 0 to 38 mm gives an increase in CO_2 carried in the plasma from 0 vols. to 50 vols per cent If the CO_2 were in simple solution, this change of tension would raise the CO_2 content only to 2½ vols per cent. The co-existence of other weak salts of sodium, such as phosphate or albuminate, with the carbonate has the effect of rendering the latter more unstable and more susceptible to changes in mass action of CO_2, *i e* to changes in the CO_2 tension.

This struggle between the CO_2 and the weak acids of the serum for the possession of the sodium is constantly going on. In the tissues, where the CO_2 tension is high, the mass influence of this acid predominates, and a large amount of it is taken up into the blood, where it forms sodium bicarbonate. It is difficult to be certain of the tension of the carbon dioxide in the cells themselves. In urine it is 9 per cent., and in bile 7 per cent. It may be estimated in the tissues of the intestinal wall of an animal such as the rabbit, with a thin-walled gut, by injecting air into a ligatured loop of intestine, and analysing the air after two or three hours. The air is then found to contain 7 to 8 per cent. CO_2. Thus the tension is much higher in the tissues than even in the venous blood, and there must be a continual flow of CO_2 from tissues to lymph, and from lymph to blood-plasma.

We have seen above that the taking up of oxygen by the blood in the lungs can be explained on purely physical grounds, since the tension of oxygen in the alveoli is sufficient to cause almost complete saturation of the hæmoglobin. Our experimental data however do not yet suffice to show that the physical conditions at work account for the giving off of CO_2 to the air in the alveoli. In order that this might happen by a mere process of gaseous diffusion, the following conditions must be present.

The tension of the carbon dioxide in the pulmonary alveoli must always be less than that in the blood. If this be so, the blood in its passage through the pulmonary capillaries will give off CO_2 to the alveolar air, and the CO_2 tension in the blood will be diminished. But this discharge of CO_2 can never go on to such an extent that the CO_2 tension in the blood should fall below that in the alveolar air; for if this were the case there would be at once a retrograde movement of the CO_2, which would then pass from the alveolar air back to the blood. Thus the CO_2 tension in the blood of the pulmonary vein can never be less than that of the alveolar air.

The experimental investigation of this question is not entirely satisfactory. According to Pflüger and Frédéricq, the output of carbon dioxide as well as the intake of oxygen in the lungs can be accounted for by simple processes of diffusion. The basis for this statement lies in the determination by aerotonometric methods of the tensions of oxygen and CO_2 in venous blood, in arterial blood, and in alveolar air. The average results obtained by these methods are as follows:

Arterial blood	2.8 per cent	from dog[1]
Venous blood	3.5—5.4 per cent	
Alveolar air	2.8 per cent.	

It would seem from these figures that the interchange of gases in the lungs was practically complete, and such a result is not surprising when we consider that the surface area of blood exposed in the alveoli of the lungs amounts to 2,000 square feet, every blood-corpuscle being practically exposed on two sides to the alveolar air.

Objections have however been raised to these results. It has been pointed out that the tension of oxygen in the blood, even in the arteries, must be constantly and rapidly diminishing as the blood leaves the lungs, while the tension of CO_2 must increase in a like manner, although to a less degree, since it is found that any delay in the pumping of the gases out of the blood leads to a diminution of total oxygen and to an increase of CO_2. This slight loss of oxygen, in consequence of processes of oxidation going on in the blood itself, would cause a considerable change in the oxygen tension, and must therefore diminish the value of the results obtained by the aërotonometer. In order to avoid this source of fallacy, Haldane has devised a method of determining the oxygen tension of the blood in the lungs, founded on the use of carbon monoxide.

It has already been mentioned that carbon monoxide has the power of displacing oxygen from oxyhæmoglobin to form a much more stable compound, carboxyhæmoglobin. If blood be shaken up with a mixture of oxygen and carbon monoxide, the hæmoglobin distributes itself between the two gases. In order however to get an equal distribution, it is necessary to take a very small percentage of carbon monoxide, owing to its greater avidity for hæmoglobin. Thus if hæmoglobin solution be shaken up with air containing 0.07 per cent of CO, the result is a mixture of equal parts of oxy- and carboxyhæmoglobin. The affinity of CO for hæmoglobin would thus appear to be about $\frac{21}{0.07} = 300$ times the affinity of oxygen for hæmoglobin.

Carbon monoxide however is not destroyed in the body, so that if a mixture containing a small proportion of CO be breathed, this gas will be taken up until a certain percentage of hæmoglobin is converted into CO hæmoglobin and the tension of CO in the tissues and fluids of the body is equal to that of the inspired air. The amount of hæmoglobin therefore, which is converted into carboxyhæmoglobin, will serve as a measure of the relative tensions of CO and oxygen in the lungs. If the oxygen tension of arterial blood were the same as that of air, we should expect that, with a given percentage of CO in the air breathed, the final saturation with CO of the blood within the body would be the same as the saturation of blood when shaken outside the body with air containing the same percentage of CO as in the air breathed It was found by Haldane however that in all cases the percentage of CO hæmoglobin formed was much less in the body than outside the body. Thus in blood shaken up with air containing 20 9 per cent oxygen and 0·045 per cent CO, the amount of carbon monoxide formed was 31 per cent of the whole hæmoglobin When the same mixture was inhaled for three or four hours by a man, the percentage of CO hæmoglobin in his blood rose only to 26 per cent, at which figure it remained stationary. This would correspond to an oxygen tension of about 25 per cent. of an atmosphere, whereas we have already seen that the oxygen tension in the alveoli cannot be greater than 15 per cent. Hence it would appear that the epithelial cells of the alveoli play an active part in the respiratory interchange, taking up the oxygen on one side at a tension of 15 per cent and piling it up on the other until the pressure in the blood is double that in the alveolar air.

---

[1] The dog in these experiments was curarised, and artificial respiration was employed. On this account the amounts of CO_2 in the expired air and in the blood were reduced below normal.

Theoretically there is no reason to deny the possibility of such powers to the pulmonary epithelium We know that the secreting cells of the kidney take up urea from the blood which contains only about 0 05 per cent of this substance and excrete it into the renal tubule, into a medium containing about 2 per cent, and if the data given by Haldane are correct, we must ascribe an analogous function to the pulmonary epithelium These data however were obtained by a colorimetric method working with very minute quantities of blood, and in the absence of further control experiments the question must be regarded as undecided.

I have already mentioned that part of the carbon dioxide in the blood is in combination with the red blood-corpuscles. A solution of hæmoglobin is also found to have a power of combining with CO_2 to form a loose chemical compound. It is thought by some that this carbon dioxide hæmoglobin acts as a carrier of CO_2 between the plasma and the alveolar air, and that, under the influence of the oxygen of the alveolar air, the CO_2 is expelled from the corpuscles, causing a sudden rise of CO_2 tension in the plasma, and therefore a discharge of this gas into the alveoli.

SECTION 3

THE REGULATION OF RESPIRATION

For the normal carrying out of respiration a complicated series of co-ordinated movements is necessary. And this is not all. The respiratory movements must be adjusted in rhythm and strength to the varying needs of the organism. When the animal is performing active work, when the muscles of the body are contracting vigorously and producing large quantities of carbon dioxide, the respiratory movements must be also quickened and deepened in order to provide for the due aeration of the blood, and the discharge of the excess of carbon dioxide produced.

This co-ordination of the activities of the respiratory muscles and their adaptation to the varying needs of the organism are brought about through the agency of the nervous system, and in particular by a circumscribed portion situated in the medulla oblongata.

If a section be made just above the pons dividing the brain from the lower parts of the central nervous system, it will be observed that the respiratory movements go on normally.

If another section be made at the lower border of the medulla, the diaphragm and ribs will be motionless, but respiratory movements may be still observed to take place in the facial muscles and larynx. These experiments show that the part of the nervous system presiding over the movements of respiration is situated somewhere between the two sections. This 'centre' can be localised still more exactly. Injury to a small portion of the medulla in the immediate neighbourhood of the nuclei of the vagus nerves, and just below the vaso-motor centre, causes total cessation of respiratory movements and death of the animal. Hence this part of the nervous system was called by Flourens, its discoverer, the *nœud vital.*

In new-born animals a few abortive attempts at respiration are sometimes observed even after destruction of this centre ; and it is therefore supposed that there are subsidiary centres in the cord controlled and regulated by the centre in the medulla. This is true, since the anterior cornual cells, whence the motor fibres to the respiratory muscles arise, are situated all the way down the cord. But these are not *respiratory* centres, since respiration involves a co-ordination of the various motor centres. The spasmodic movements that may occur under the influence of strychnine or asphyxia after destruction of the medulla are not co-ordinated, inspiratory and expiratory muscles contracting at irregular intervals and in many cases simultaneously.

The question now arises whether the activity of this centre in the medulla may be regarded as automatic or reflex: that is to say, do the rhythmic discharges proceeding from it depend merely on local changes taking place in the centre, induced perhaps by changes in the surrounding lymph or blood, or on a rhythmic or continuous excitation of the centre by stimulation of some afferent nerve? If the vagus nerves be cut and the spinal cord divided just below the medulla, respiratory movements of the alæ nasi are seen to continue and to grow more pronounced as the blood becomes venous in consequence of the cutting off of the chief respiratory muscles from the medullary centre.

A still more thorough isolation of the centre has been accomplished by dividing the vagi, cutting through the upper part of the medulla and through the cord at the first dorsal nerve, and then dividing all the cervical posterior roots. In this case movements of the diaphragm still continued, but consisted simply in a series of prolonged spasms, at first about two to four per minute and gradually getting less frequent till the animal died. We might argue from this that the centre was capable of a very imperfect degree of automatic action, but needed the stimulus of afferent impulses from the vagi or from the higher parts of the brain to render these actions adequate for the respiratory needs of the organism.

In the above experiment the centre cannot be regarded as free from all afferent stimuli, since the mere closure of the demarcation current in the cut ends of the nerves would cause a certain amount of excitation, and the animal does not survive sufficiently long to allow this condition to pass off. Hering has shown that in the 'spinal cord frog' (i.e. one in which the brain has been destroyed) section of all the posterior roots absolutely destroys all mobility, the injection of strychnine being without effect. A typical spasm however can be at once produced by exposing and stimulating the stump of one of the cut posterior roots. We might suppose that the respiratory centre would be similarly devoid of automatism if absolutely free from afferent stimuli.[1] It can be shown however that the centre tends to respond to all stimuli, continuous or rhythmic, by means of rhythmic discharges

Whether or no we accept as proved the possible automatism of the centre, there is no doubt that the activity of the centre is intimately dependent on its local chemical state or environment.

If, the nervous centres being intact, the proper aeration of the respiratory centre be interfered with in any way, as by obstruction of the respiratory passages, or by perforation of both pleuræ, or by ligature of all the arteries to the brain, or by extensive loss of blood, the respiratory movements increase in strength and frequency, and if the disturbing factor be not removed the animal dies, presenting a train of phenomena which are classified together under the term 'asphyxia.'

The phenomena of asphyxia may be divided into three stages

(1) In the first stage, that of hyperpnœa, the respiratory movements are increased in amplitude and in rhythm. This increase affects at first both inspiratory and expiratory muscles. Gradually the force of the expiratory movements becomes increased out of all proportion to the inspiratory, and the first stage merges into:

(2) The second, which consists of expiratory convulsions, in which almost every muscle of the body may be involved. Just at the end of the first stage consciousness is lost, and almost immediately after the loss of consciousness we may observe a number of phenomena extending to almost all the functions of the body, some of which have been already studied Thus at this time the vasomotor centre is excited, causing universal vascular constriction. There is often also secretion of saliva, inhibition or increase of intestinal movements, constriction of the pupil, and so on.

(3) At the end of the second minute after the stoppage of the aeration of the blood, the expiratory convulsions cease almost suddenly, and give way to slow deep inspirations. With each inspiratory spasm the animal stretches itself out.

---

[1] According to Sherrington, it is possible to excite strychnine or asphyxia spasms in a dog or cat with isolated spinal cord, in which all the afferent roots below the transection have been divided six or seven hours previously These experiments appear to indicate that in the *mammal* the motor nervous mechanisms can be set into activity apart from the incidence of afferent impressions.

and opens its mouth widely as if gasping for breath. The whole stage is one of exhaustion; the pupils dilate widely, and all reflexes are abolished. The pauses between the inspirations become longer and longer, until at the end of four or five minutes the animal takes its last breath.

Somewhat similar movements of respiration, but on a smaller scale, may be produced by increasing the activity of the centre, and therefore its gaseous interchanges, by warming the blood in the carotid arteries on its way to the brain. Under these circumstances there may be a considerable quickening of respiration unaccompanied by any deepening, which is often spoken of as *tachypnœa*. On the other hand, we may slow the respiratory movements by placing a small piece of ice on the floor of the fourth ventricle.

In the production of the phenomena of asphyxia two factors must be at work. In the first place there is an accumulation of carbon dioxide in the blood bathing the centre or an increased tension of this gas in the centres themselves, either as a result of deficient excretion or increased production. On the other hand, the centre is deprived of oxygen, either by failure of renewal of the oxygen supply, or by increased using up of this gas in the metabolism of the centre. The question arises, Which of these two changes is responsible for the different physiological events which characterise asphyxia? At various times these phenomena have been ascribed either to the increased tension of CO_2 or to the diminished tension of oxygen in the centre. As a matter of fact, both factors are at work, and we must now proceed to discuss the exact part played by each. In order to investigate this point we may try the effect on the respiratory movements of altering the tension of these two gases in the air breathed. The results of such experiments are very striking. It is found that even a slight increase in the percentage of CO_2 in the air causes an increase first in the depth and later on in the rhythm of respiration. This is well shown in the following Table by Haldane, which represents the average depth and frequency of the respirations when the subject was breathing normal air and air charged with varying percentages of CO_2. It is seen that a rise of CO_2 in the atmosphere to 2 per cent. increases the depth of respirations by 30 per cent, and the total alveolar ventilation by 50 per cent. A rise of CO_2 to 3 per cent increases the total ventilation of the alveoli by 126 per cent. An amount of CO_2 equivalent to 6 per cent. increases the depth of each respiration by 272 per cent., and the total alveolar ventilation by 757 per cent.

Percentage CO_2 in inspired Air	Average depth of Respirations	Average frequency of Respirations per Minute	Ventilation of Alveoli with inspired Air. (Normal =100)	CO_2 Percentage in Alveolar Air
0·04	673	14	100 (6·60 litres per min.)	5·6
0·79	739	14	116	5·5
2·02	864	15	153	5·6
3·07	1,216	15	226	5·5
5·14	1,771	19	498	6·2
6·02	2,104	27	857	6·6

If we examine the last column of figures in this Table, representing the percentage of CO_2 in the alveolar air, it will be seen that, in spite of the very large variations in the air breathed, the alveolar content in CO_2 remained practically constant until the CO_2 in the atmosphere was increased to such an extent that the processes of compensation were no longer efficient. We must conclude therefore that the respiratory centre is so arranged as to react to the slightest increase of CO_2 tension in the blood, any increase in this gas giving at once a compensatory increase in depth and frequency of respiration, so that the alveolar CO_2 content may be maintained almost constant.

That it is the tension of CO_2 in the alveolar air, and therefore in the blood bathing the centres, and not the percentage amount of this gas, which is the determining factor, is shown by a comparison of the composition of the alveolar air under different atmospheric pressures. Thus, when the subject of the experiments, from which the above Table was derived, was placed in an air-chamber compressed to a pressure of 1,261 mm., the mean percentage of CO_2 in the alveolar air was 3·42, corresponding, however, to a tension of 5·6 per cent. of an atmosphere, a figure almost identical with those given in the last column of the Table above. At the top of Ben Nevis, where the barometric pressure was 646 mm. the percentage of CO_2 in the alveolar air was 6·6, corresponding to a tension of 5·2 per cent. of an atmosphere, *i.e.* of 760 mm.

Thus the pressure of CO_2 in alveolar air remains practically constant with widely varying limits of atmospheric pressure and with very different percentages of CO_2 in the inspired air, showing that the reactions of the organism are directed so as to maintain, by alterations in the respiratory depth and rhythm, a constant *tension* of this gas in the alveoli.

Very different are the phenomena observed on alteration of the partial pressure of oxygen. Here, within wide limits, the partial pressure of oxygen in the alveolar air is determined by its pressure in the inspired air. Thus, if we take the same series of observations, with a pressure of 646 mm., the percentage of oxygen in the alveolar air was 13·19, corresponding to a tension of 10·4 per cent. At an atmospheric pressure of 755 mm. the percentage of oxygen in the alveolar air was 13·97, corresponding to a tension of 13·06 per cent. In air compressed to a pressure of 1,260 mm. the percentage of oxygen was 16·79, corresponding to a tension of 26·8 per cent. of an atmosphere of 760 mm. The same sort of results are obtained by altering the percentage of oxygen in the air breathed. It is found that the oxygen tension or percentage in the inspired air can be lowered from its normal of 20·93 to 12 or 13 per cent. without altering in any way the depth or rhythm of respiration, and in fact without any change being noticed by the individual who is the subject of the experiment. A percentage of 13 per cent. of oxygen corresponds to an alveolar content in oxygen of 8 per cent., and with a further reduction of the oxygen content there is increased pulmonary ventilation, but the diminution in oxygen may be pushed to such an extent that the patient becomes blue from the deficient aeration of his hæmoglobin, without any considerable distress being caused. In fact, in many cases, the subject of such an experiment may lose consciousness suddenly, before he has been aware of any serious deficiency in his aeration. We must conclude, therefore, that the respiratory centre possesses a specific excitability for carbon dioxide, and that it is by this specific excitability that the normal depth and rhythm of the respiratory movements are determined. The uses of such an excitability to the organism are obvious.

We may take as an example the changes in respiration which occur in an animal as the result of muscular exercise.

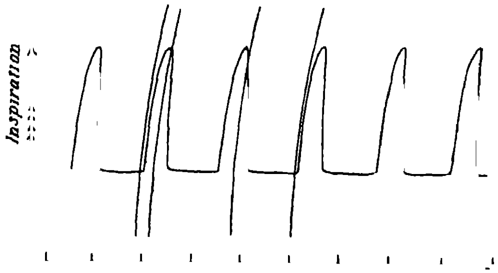
Under normal circumstances any changes in the amount of oxygen in the air breathed will be of the rarest possible occurrence. As the result of muscular exercise a large amount of carbon dioxide is produced in the muscles. The venous blood passing from the muscles to the lungs will therefore be more highly charged with this gas, and a rapid rise in the alveolar CO_2 pressure, and therefore in the arterial CO_2 pressure, will be occasioned. The respiratory centre is thus stimulated to increased activity, with consequent lowering of the alveolar CO_2 pressure, until a point is reached at which an equilibrium is maintained between the effect of the increased production of CO_2 in raising the arterial CO_2 pressure and that of the increased respiratory activity in lowering it.

In certain experiments by Zuntz and Geppert on the causation of the increased respiratory movements during muscular exercise, these observers found that the movements were increased to such an extent as to bring the amount of CO_2 in the arterial blood below the normal In these experiments, however, the muscular contractions were not produced by normal exercise, but were obtained by tetanising through the spinal cord the lower limbs of an animal Under these circumstances, the activity of the muscle would be associated with a diminished blood-flow, so that the contractions would be carried out in the absence of a sufficient amount of oxygen As we have seen earlier in dealing with the metabolism of muscle, in the absence of sufficient oxygen, muscular contractions result in the production, not of CO_2, but of lactic acid, and it is highly probable that, in the experiments in question, there was a discharge of acid substances into the blood, diminishing the alkalinity of this fluid and therefore lowering its carrying power for CO_2 As a matter of fact, one can produce dyspnœa by diminishing the alkalinity of the blood by the injection of acids, and attacks of dyspnœa are observed in the later stages of diabetes, when the alkalinity of the blood is decreased in consequence of the enormous production of such bodies as oxybutyric acid. A diminished carrying power of the blood for CO_2 will necessarily raise the tension of this gas in the tissues where it is formed, and a diminished alkalinity of the blood will therefore tend to cause a higher tension of CO_2 around the respiratory centre It is probable that when muscular exercise is carried to exhaustion, this diminishing of alkalinity of the blood also plays its part in the hyperpnœa and dyspnœa, but in every case the determining factor seems to be the increased tension of the CO_2 in the respiratory centre itself We must therefore conclude that the depth and rhythm of respiration—that is, the regulation of the rate of alveolar ventilation and of respiration—depend under normal conditions on the CO_2 pressure in the respiratory centre This part of the central nervous system has developed a specific sensibility for CO_2, a rise of 0·2 per cent of an atmosphere in the tension of this gas in the alveoli, and therefore in the arterial blood, being sufficient to double the amount of alveolar ventilation during rest

It is only the first phase in the phenomena of asphyxia which is thus conditioned by the changes in the CO_2 tension. The respiratory centre shares with the rest of the central nervous system a sensitiveness to the absence of n, deprivation of oxygen having first an excitatory and later a paralytic ect In asphyxia the first centres to feel this effect are those of the cortex, d during the first stage there is mental excitation terminating rapidly in abolition of consciousness at the end of this stage. During the second stage here is a discharge of energy, which spreads throughout the whole nervous system, beginning in the bulbar centres and causing a great rise of blood pressure with slowing of the heart, and extending thence to all the spinal centres with the production of muscular spasms At this stage, too, there is a discharge of impulses giving contraction of the pupil, and a little later discharge along the whole sympathetic system producing the various phenomena of vaso-constriction, erection of hairs, sweating, salivation, which are generally brought about by stimulation of different parts of this system. The phenomena of the third stage are due to a gradual exhaustion of the nerve-centres, accompanied or preceded by an exhaustion and dilatation of the heart, the circulation failing before the excitation of the lower centres has entirely come to an end In this third stage, however, it is impossible by the strongest stimuli to evoke any reflex, and the general phenomena are those of exhaustion.

Although we must regard the specific sensibility of the respiratory centre to CO_2 as the most important factor in determining the depth and rhythm of the respiratory movements, these movements and the condition of the respiratory centre itself are modified in a large degree by impulses arriving at the centre along both vagi. Through other sensory nerves of the body the respiratory movements can be altered reflexly, but it is only through the vagi that a continuous stream of impulses passes to the centre under normal circumstances, so that every respiratory movement is modified by these impulses.

Fig. 194

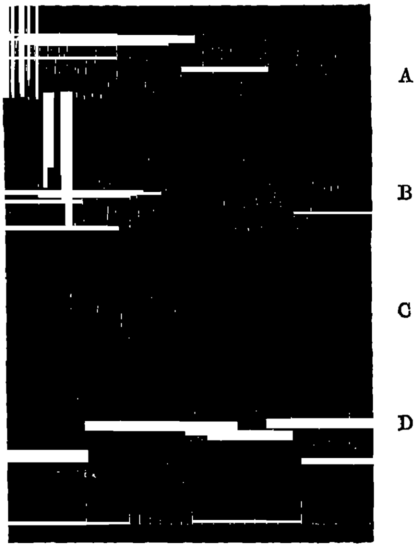


Normal tracing of diaphragm slip (Head's method)

In studying the nervous mechanism of respiration, it is necessary to have some accurate method of recording the respiratory movements. They may be registered by means of a tambour applied to the chest, communicating with another tambour provided with a lever, which is arranged to write on a blackened surface, or a side tube to a cannula in the trachea may be connected with the registering tambour In the first case, movements of the thorax are registered, in the second, changes of intra-pulmonary pressure hese methods are obviously useless when it is wished to study the effects of rtificial distension or collapse of the lungs. In this instance we may use the igenious method described by Head In the rabbit a slip of the diaphragm n either side of the ensiform cartilage is so disposed that the end of it may be eed and attached by a thread to a lever without injury to its blood- or nerve-upply It is found that this slip contracts synchronously with the rest of the iaphragm, so that it serves as a sample of the diaphragm, the contractions of hich may be recorded uninfluenced by passive movements of the chest-wall or rtificial increase of intra-pulmonary pressure.

If, while the respiratory movements are being recorded n one of the aforementioned ways, both vagi be divided,[1] a narked change in the respiratory rhythm is at once seen (Fig. 195). The first effect is an increased inspiratory tonus, but this rapidly disappears, and the respiratory movements

Fig. 195.



Tracings of respiratory movements—A Normal B After division of one vagus. C After section of both vagi D Both vagi cut. The central end of one vagus stimulated with weak induced current at Exc

Lower line = time-marking, indicating seconds. (From Waller) become less frequent and are increased in amplitude. If now the central end of one of the vagi be stimulated with an interrupted current, the respiration may be quickened (as in the experiment represented in Fig. 195), or, as is more commonly the case, the inspiratory movements may be increased at the expense of the expiratory, so that finally a condition of inspiratory standstill is produced, and the slip of the diaphragm enters into prolonged contraction.

---

[1] The division of the vagi is best effected by putting them on a hooked copper wire, of which the upper end is inserted in a freezing mixture. In this way complete functional division of the nerves is obtained without any excitation. If the nerves be cut, a certain amount of stimulation takes place in consequence of the closure of the demarcation current produced by the cross-section.

With a very weak stimulus it is sometimes possible to produce augmentation of the *expiratory* movements or rather inhibition of the inspiratory, and this is the invariable result of passage of a *constant* current through the vagus in an ascending direction. This effect however may be more strikingly brought about by stimulation of the central end of the superior laryngeal nerve. Excitation of this nerve produces first an inhibition of inspiration, so that the respiratory muscles come to a standstill in the position of expiration, and then a forcible contraction of the expiratory muscles takes place This illustration of the presence of expiratory fibres in the superior laryngeal nerve is not confined to laboratory experience, but is constantly occurring in everyday life The superior laryngeal nerve supplies sensory fibres to the mucous membrane of the glottis, and we know that the slightest irritation of these fibres—the presence of a crumb or a particle of mucus—causes forcible expiratory spasms, with spasmodic closure of the glottis, which we term a cough [1]

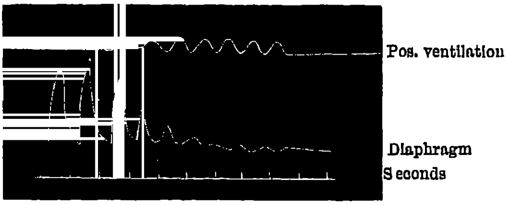
So we see that the vagus nerve contains two kinds of afferent fibres, or at any rate afferent fibres with two distinct functions. Stimulation of the one kind stops inspiration and produces expiration; stimulation of the other stops expiration and produces inspiration.

Since section of both vagi causes slowing of respiration, it is evident that, under normal circumstances, impulses which exert some influence on the respiratory centre and quicken respiration, must travel up the vagi from the lungs. The respiratory movements cause an alternate distension and contraction of the lungs, and it has long been thought that it is these changes in the volume of the lungs which start the accelerating impulses that travel up the vagus nerves. To test the truth of this hypothesis it is necessary to study the two phases of respiration separately; that is, to see first the result on the respiratory impulses of repeated distension of the lungs, and secondly the result of a sudden collapse or a contraction caused by sucking air out of the lungs. The first mode of experiment, when air is driven repeatedly into the lungs, is spoken of as *positive* ventilation; and the second, when air is sucked repeatedly out of the lungs, as *negative* ventilation. In these experiments it is advantageous to employ Head's method of registering the diaphragmatic movements. If, in a rabbit breathing quietly, air be repeatedly blown into the lungs, the inspiratory movements, as evidenced by the contraction of the diaphragm, are gradually knocked down, till finally the animal is in a condition in which no inspiratory movements whatever are made (Fig. 196); or the diaphragmatic standstill may be followed by a strong contraction of the expiratory muscles. Thus distension of the lungs has the same effect as stimulation of the superior laryngeal nerve in stopping inspiration and producing expiration.

---

[1] It must not be imagined that the fibres of the superior laryngeal nerves are concerned in the reflex maintenance of the normal respiratory rhythm They are cited here merely because the result of their stimulation resembles that which would be caused by stimulation of the analogous expiratory fibres which run in the trunk of the vagus from the *lungs* to the respiratory centre

FIG 196



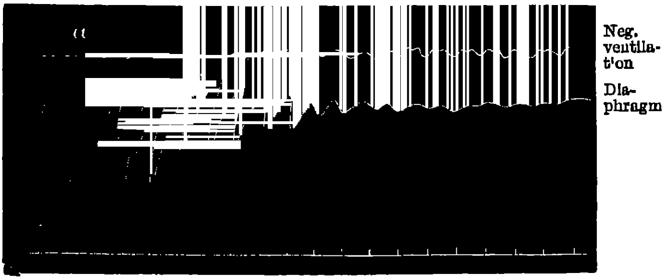
Positive ventilation (Head). Under the influence of positive ventilation, the inspiratory contractions of the diaphragm become less and less till they disappear completely

If, on the other hand, air be sucked out of the lungs at regular intervals (negative ventilation), the movements of the diaphragm are amplified, and it does not relax completely after each individual respiration. The relaxation becomes more and more incomplete, until finally the diaphragm enters into a condition of continued contraction, which may last for several seconds (Fig. 197). Thus collapse of the lung inhibits expiration and augments inspiration.

The effects of distension or collapse of the lung may be still more readily shown by simply closing the trachea at the end of inspiration or of expiration. The results of such an experiment are shown in Fig. 198.

These experiments throw complete light on the quickening action of the vagus on respiration. Normal respiration is a series of reflex acts. Each inspiratory movement causes an expansion of the lung, which in its turn stimulates the vagus nerve-endings, inhibiting the movement which has given rise to the stimulus, and causing the ensuing expiratory movement. The collapse of the lung attending expiration acts like the negative ventilation in the experiment above mentioned in stimulating the inspiratory nerve-endings of the vagus; and the impulse thus produced acting on the medullary centre checks the expiratory and hurries on the inspiratory movement. In this way, under normal circumstances, the rhythm of the respiratory centre is determined reflexly through the agency of the vagi, while the chief factor in determining the total pulmonary ventilation, *i.e.* the depth of the movements, is the CO_2 tension of the blood

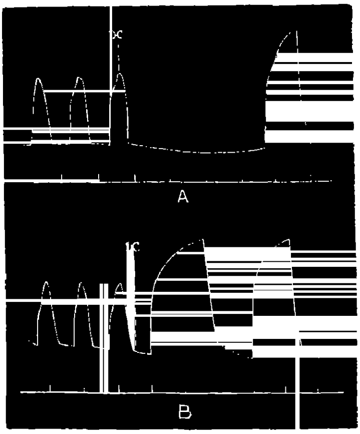
FIG. 197



Negative ventilation (Head). At *a* negative ventilation was commenced The expiratory relaxation of the diaphragm is seen to become more and more incomplete, until it finally enters into continued contraction.

In the foregoing account we have spoken of the expiratory and inspiratory effects of the vagus as if they were of equal importance. It seems probable however that the inhibitory or expiratory impulses started by the inspiratory movement, the only active part of normal respiration, play a more prominent part in the regulation of respiration than do the inspiratory impulses; and one observer (Gad) goes so far as to deny altogether the existence of two kinds of respiratory fibres in the vagus According to Gad, the vagus, as regards the respiratory centre, is a purely inhibitory nerve. Hence the primary effect of dividing both vagi is an increased inspiratory tone This view at first seems paradoxical, in that it explains the final slowing of respiration after section of the vagi as due to the cutting off of previous inhibitory impulses But inhibition in all tissues has a twofold effect Although the immediate effect is diminution of activity, yet the diminished disintegration necessarily associated with diminished activity means an increase of the anabolic at the expense of the katabolic processes of the tissues In this way we explained the diminished excitability occurring in a nerve at the anode of a constant current, and it will

FIG 198



Effects of distension—collapse of lung Both curves are described by a lever attached to a slip of the diaphragm of a rabbit A contraction of the diaphragm (inspiration) raises the lever, during relaxation of the diaphragm the lever falls

In A, the trachea is closed at x, the height of inspiration, a pause follows, during which the lever gradually sinks until an inspiration (a very powerful one) sets in

In B, the trachea is closed at the end of expiration, x, there follow powerful inspirations (From Foster)

be remembered that the secondary result of anelectrotonus was increased irritability and consequent excitation at break of the constant current The same sort of process must occur in the respiratory centre A continued restraint of its rhythmic activity must lead to a heaping up of its irritable material, so that the final result is a state of hyperexcitability in which the centre, so to speak, boils over on the slightest provocation

In this condition a cutting off of the inhibitory impulses must at first increase the activity of the centre leading to the increased inspiratory tonus already described But unchecked by any reining impulses, the centre enters upon a career of spendthrift activity Each inspiratory contraction is maximal, but the centre, exhausted by the effort, has to wait a considerable time before it can accumulate sufficient energy for the next, hence the final result of section of both vagi is deepening and slowing of respiration In the normal state we must imagine that the function of the vagus is to increase the excitability of the respiratory centre, and so make it more susceptible to slight changes in the CO_2 tension of the blood

Although Gad has rendered great service in emphasising the importance of the inhibitory or expiratory impulses which ascend the vagi, there is no doubt that he went too far in denying the existence of inspiratory fibres in the vagus This is shown by the following experiment of Head. According to Gad's view, collapse of both lungs implies simply a removal of the normal inhibitory impulses ascending the vagi, and is therefore equivalent to division of these two nerves If in the rabbit the left vagus be divided, a tube can be introduced into the left bronchus and artificial respiration can be performed by alternate inflation and collapse of the left lung, without in any way affecting the respiratory centre, all connections with the latter being destroyed (*v* Fig 199)

FIG. 199

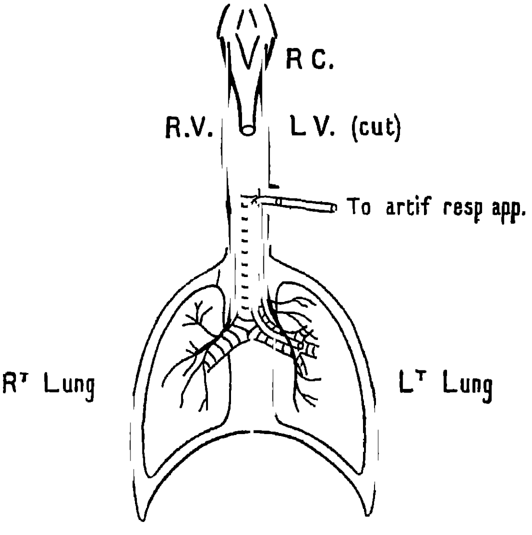
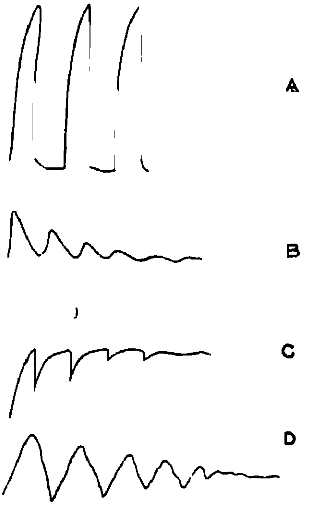


Diagram to illustrate Head's experiment on the effect of collapse of the lung R C., respiratory centre , R V , L V , right and left vagi

Meanwhile the animal carries out normal respiratory movements, which can be recorded by the diaphragm slip method While the slip is contracting regularly, the right pleura is opened and the right lung allowed to collapse. The effect of this collapse carried up by the right vagus to the centre is an extreme contraction of the diaphragm, and since the onset of asphyxia is prevented by the artificial respiration carried out on the left lung, the tonic standstill of the diaphragm may last over a minute In this case therefore, the effect of collapse of one lung is enormously greater than that produced by section of both vagi, showing that the effect is due, not to abolition of the ordinary tonic inhibitory stimuli, but to excitation of special inspiratory fibres in the vagus by the collapse of the lung

The important part played by the vagi in the regulation of normal respiration is shown still more strikingly if the respiratory centre in the medulla be separated from the higher parts of the brain before the section of the vagi is carried out. Separation of the medulla from the higher parts of the brain, as by a section just behind the corpora quadrigemina, has practically no influence on the respiratory rhythm. If now both vagi be divided, the normal respiratory movements cease entirely, being replaced by a series of inspiratory spasms, each of which lasts several seconds and is followed by a pause of half to one minute duration. These spasms are inadequate for the proper oxygenation of the blood. They become gradually less and less frequent, and the animal dies in about half an hour of asphyxia. We must conclude therefore that the respiratory centre with the help of the vagi is able to carry out normal respiratory movements. If both vagi are cut, impulses arrive at the centre from the higher parts of the brain regulating its activity, and enabling it to carry out modified but sufficient respiratory movements. Removed

FIG. 200



Different forms of apnœa produced by ventilation (Head) A Normal tracing of diaphragmatic slip, B Effect of *positive* ventilation Standstill of diaphragm in complete relaxation; C Effect of *negative* ventilation Standstill of diaphragm in a state of tonic contraction; D. Effect of combined positive and negative ventilation. Cessation of movements, the diaphragm being in a state of moderate tone from both these sources of afferent impulses, the centre discharges only a series of spasms which are totally inadequate for the renewal of the blood gases, so that the animal dies.

We may summarise these results as follows:

Respiratory centre with vagi—normal respiration.

Respiratory centre with brain—modified respiration.

Respiratory centre alone—inadequate spasmodic contractions of respiratory muscles, and death of animal.

Apnœa.—If positive and negative ventilation be used together, so that air is blown into and sucked out of the lungs at a rate quicker than the animal's respiratory rhythm, both inspiratory and expiratory processes are inhibited, and a standstill of respiration ensues. This condition is called apnœa. It has been thought to be chiefly reflex in origin, in consequence of the fact that an apnœic pause may be observed after artificial respiration for a short time with inert gases, such as hydrogen or nitrogen. The pause however does not last so long as when air or oxygen is employed, since in the former case the blood becomes so venous that the stimulation of the centre thereby produced overcomes the effects of the reflex inhibition, and a violent inspiratory movement ensues.

One factor that has not been sufficiently allowed for in these ventilation experiments is the effect that rapid ventilation with any gas will have in reducing the CO_2 tension in the blood circulating round the pulmonary alveoli, and therefore round the respiratory centre. The respiratory centre has a specific sensibility to CO_2, while it shares with the rest of the medulla and cord the susceptibility to absence of oxygen. Hence any change in the amount of CO_2 in the air breathed (irrespective of changes in the oxygen) produces corresponding changes in the respiratory rhythm. If for instance a man be made to breathe a mixture of oxygen, nitrogen, and CO_2, containing the ordinary percentage of oxygen (21 per cent.), but 2 or 3 per cent. of CO_2, he experiences a feeling of breathlessness, and objectively the respiratory movements are increased in rhythm and extent (hyperpnœa) so as to keep the CO_2 tension in the alveolar air, and therefore in the blood, at its normal point. If the CO_2 content be increased to about 4·5 per cent., it is impossible to produce an apnœic pause, however rapidly the respiratory movements be carried out. It would seem, therefore, that ordinary apnœa is entirely due to deficiency of CO_2 tension in the respiratory centre, and that although the vagus nerve is inhibitory of respiration, it is impossible to summate a series of vagus inhibitions by artificial respiration so as to produce a lasting cessation of respiratory movements. The chief use of the vagi, in fact, in respiration seems to be for maintaining by frequent inhibitions the excitability of the respiratory centre at a maximum.

We have seen that if a man breathe a mixture of nitrogen and oxygen free from CO_2, and the oxygen be gradually diminished, no feeling of 'want of breath' may be experienced. Respiration is often practically unaltered, although the deficient oxygenation of the blood may be shown by the blueness of the lips and face. In certain cases great oxygen deficiency excites the respiratory centre, but in many cases no ill effects may be felt by the subject before he suddenly becomes unconscious from lack of oxygen. Immediately following this loss of consciousness may come the convulsive phenomenon of asphyxia.

From the lack of any mechanism in the respiratory centre to respond to minute changes in the oxygen tension of the surrounding atmosphere, it follows that any diminution in oxygen tension (as by change of altitude) must cause a corresponding diminution in the degree of saturation of the hæmoglobin of the blood with oxygen. This change in oxygen saturation is at once felt by the blood-forming organs; so that a change of habitation from a low-lying to a mountain district is followed by an increased production of blood corpuscles, until the oxygen carrying capacity of the blood is the same at the lower oxygen tension as it was previously at the higher oxygen tension of the plains.

Broncho-motor functions of the vagus—The unstriated muscular fibres, which form a prominent element in the walls of the bronchioles, receive fibres from the vagi which are efferent in function If positive ventilation under a constant pressure be maintained in an animal and the excursions of the chest-wall recorded, a perfectly regular series of movements are obtained, which serve as a measure of the expansion of the lungs under each inspiratory blast of air If now the peripheral ends of both vagi be stimulated, the excursions of the lever at once are diminished in extent, showing that the air does not enter and expand the lungs with its former freedom The vagi in fact are the motor nerves to the bronchial muscle Stimulation of these nerves therefore causes occlusion of the smaller air-tubes and diminished entry of air into the lungs The attacks of dyspnœa which characterise asthma are due to spasmodic contraction of the bronchial muscle, probably in consequence of abnormal stimulation of the central origin of the vagi.

Changes in Composition of Air breathed

The oxygen tension of the air can be considerably reduced without causing inconvenience. If however a mammal be exposed to air at a pressure of 300 mm. (corresponding to a partial oxygen pressure of 60 mm. Hg), it becomes dyspnœic and dies of asphyxia. The experience obtained in balloon and mountain ascents is in complete harmony with the result of this experiment. Dyspnœa does not begin till a height of 5,000 metres is reached, which corresponds to a mercurial pressure of 400 mm. Hg

It is interesting however to note that the extreme dyspnœa with which mountaineers are attacked at a height of about 5,000 metres passes off after some time, and then they may pursue their way another 1,000 metres higher without any discomfort (Whymper). In view of the results given on p. 394, it seems at first difficult to explain the deleterious effects of high altitudes or reduced oxygen pressures. It was there mentioned that even at a partial pressure of oxygen of 25 mm. Hg (corresponding to an atmospheric pressure of 119·3 mm. Hg, or to a height above the sea of about 14,000 metres), as much as 73·3 per cent. of the hæmoglobin was converted into oxyhæmoglobin, and yet dyspnœa is produced at a height of 6,000 metres, corresponding to a pressure of 358 mm. (75 mm. oxygen). We must remember however that an important factor in the respiratory exchanges is the *rapidity* of passage of oxygen from air to blood. The blood is constantly circulating through the lungs, and during the short time of its passage becomes nearly saturated with oxygen. The velocity of passage of oxygen across the epithelial membrane will vary directly as the difference of pressure on the two sides of the membrane. As this difference diminishes, the organism seeks to increase the velocity of passage by increasing the area of lung surface, *i e.* by deepening of the respiratory movements. At the same time there is quickening of the heart's action and increased velocity of blood-flow so as to increase the amount of oxygen carried by the blood in a given time. These processes of compensation however cannot go on indefinitely, and distress, which is chiefly circulatory in character, begins to be experienced when the limit of compensation is arrived at. This limit occurs in trained men at an atmospheric pressure of about 400 mm. Hg; and it is of course reached sooner if the respiratory needs of the organism are increased by severe muscular exercise (as in mountain climbing). The gradual accustoming to heights, which is a common experience, is a complex phenomenon, due partly to training of respiratory and heart muscles, and partly to an increase of red corpuscles and hæmoglobin contents of the blood. It is probable that the dwellers in mountain regions, such as the lofty South American plateaus of Potosi, Quito, etc., would be found to have a greater lung area per unit body weight than the dwellers on the plains.

If the oxygen in the air supplied to an animal be reduced to 3 per cent., it rapidly dies of asphyxia with convulsions. Excess of carbon dioxide also proves fatal, but in a different manner. If an animal be placed in an atmosphere containing 6 per cent. of CO_2, after a stage of hyperpnœa it gradually becomes narcotised and dies without convulsions. CO_2 is therefore looked upon as a narcotic poison.

Gases such as nitrogen, hydrogen, and methane (CH_4) are termed *indifferent gases*. They may be respired if mixed with 20 per cent. of oxygen, and either of the other gases may be used instead of nitrogen to dilute the oxygen that we breathe, without harm or inconvenience.

Carbon monoxide is rapidly poisonous by its action on the red corpuscles. It combines with hæmoglobin, forming CO hæmoglobin, a compound which is much more stable than oxyhæmoglobin. The blood is therefore deprived of its oxygen carrier, and the animal dies of asphyxia. We have seen however that the displacement of oxygen by CO is not absolute, but only relative. Hence, although the avidity of CO for hæmoglobin is 140 times that of oxygen, we can convert the CO back into oxyhæmoglobin by increasing the mass influence of the oxygen. This may be done by giving the poisoned animal pure oxygen to breathe, or even oxygen under pressure. In pure oxygen at a pressure of two atmospheres an animal can breathe and live, even though the whole of its hæmoglobin is converted into CO hæmoglobin, the amount of oxygen which is simply dissolved by the blood-plasma being sufficient at this pressure for the respiratory needs of the animal.

Other gases which have special poisonous properties are hydrocyanic acid, sulphuretted hydrogen, phosphuretted hydrogen (PH_3), arseniuretted hydrogen, etc.

Irrespirable gases are those which are so irritating that they produce spasm of the glottis. Such are ammonia, chlorine, sulphur dioxide, nitric oxide, and many others.

Ventilation

A point of practical importance is the securing to each individual of sufficient fresh air, so that he may always have a plentiful supply of oxygen, and may be relieved of his waste products. It is found that a dwelling-room becomes unpleasant and stuffy when the percentage amount of CO_2 has reached 0·1 per cent. This stuffiness is supposed to be due to organic exhalations from the skin, lungs, and alimentary canal, some of which have a poisonous effect, giving rise to headache and sleepiness. Since these cannot be measured, it is taken as a cardinal rule in ventilation that the amount of CO_2 should never rise above 0·1 per cent. An adult man gives off about 0·6 cubic foot of CO_2 every hour. Hence in that time he raises the amount of CO_2 in 1,000 cubic feet of air from 0·04 per cent. (the normal amount in the atmosphere) to 0·1 per cent. He must therefore be supplied with 2,000 cubic feet of air per hour in order to keep the amount of CO_2 down to 0·07 per cent.

(Ordinary air contains 0·04 per cent. CO_2, therefore 2,000 cubic feet would contain 0 8 cubic foot CO_2, which with the 0·6 cubic foot given off by the man would be 1·4, which is 0·07 per cent.)

In order that the air may be easily renewed without giving rise to excessive draught, a certain amount of cubic space must be allotted to each man. Each adult should have in a room 1,000 cubic feet of space, and be supplied every hour with 2,000 to 3,000 cubic feet of air.

SECTION 4

EFFECTS OF THE RESPIRATORY MOVEMENTS ON THE CIRCULATION

The Pulmonary Circulation

Although the maintenance of the circulation through the lungs is the sole function of the right side of the heart, and so is of equal importance with the whole systemic circulation, yet owing to the simple features of this circulation it can be dealt with in a very short space. In the lungs we have an extensive system of wide capillaries presenting very little resistance to the flow of blood. The arterioles are also wide and have only a slight amount of muscular fibre in their walls, and we find therefore that the pressure necessary to drive the blood from right to left heart is also small. The determination of the normal average pressure in the pulmonary artery presents considerable difficulties, but it probably does not exceed 25 mm. Hg, *i.e.* about one-sixth of the mean aortic pressure.

The capillaries of the lungs may vary passively considerably in size according to the conditions under which they may be placed. Thus whereas at the height of inspiration the blood contained in the lungs is about $\frac{1}{12}$ of the whole blood in the body, this amount is diminished during expiration to between $\frac{1}{15}$ and $\frac{1}{18}$, and by forcible artificial inflation of the lungs may be lessened to $\frac{1}{60}$. These changes, as we shall see later, exercise a considerable effect on the systemic blood-pressure and are largely responsible for the respiratory variations observed in the systemic blood-pressure.

On the other hand this distensibility of the lung capillaries may play an important part in enabling the lungs to act so to speak as a reservoir for the left side of the heart Any temporary excess of output on the right side that, in consequence of raised arterial pressure or other factor, cannot be dealt with at once by the left heart, is taken up for a time in the lung capillaries.

Vaso-motor fibres to the lung vessels have been described as running in the anterior roots of the 3rd, 4th, and 5th dorsal nerves. Their action is however of little importance.

The Respiratory Undulations in the Systemic Blood Pressure

If we examine a tracing of the arterial blood-pressure, we notice that it presents certain periodic oscillations which accompany the movements of respiration. With each inspiration the blood-pressure rises; with each expiration it falls. The synchronism of the rise and fall with the respiratory movements is not exact, since the rise continues for a short time after the beginning of expiration, before it begins to fall, and the fall continues right into the beginning of the next inspiration, so that the highest point of the curve occurs at the beginning of expiration and the lowest point at the beginning of inspiration. During the fall which accompanies expiration, the heart-beats, as shown in the diagram (Fig. 201), become less frequent, and an obvious explanation of the fall of pressure would be to ascribe it to a reflex inhibition of the heart. On dividing both vagi, this difference in the pulse-rate during inspiration and expiration disappears, but the main features of the blood-pressure curve remain the same; so that we must look for some mechanical explanation of the respiratory undulations.

FIG 201

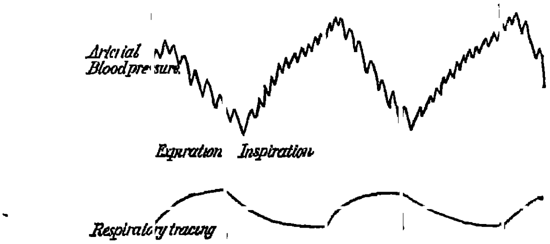


Diagram of blood-pressure curve, showing effects of the respiratory movements on blood-pressure and pulse-rate.

We have already seen that under normal conditions the lungs are in a state of over-distension, and that in consequence of this condition they are constantly tending to collapse, and are therefore exerting a pull on the chest-wall. As soon as we admit air into the pleural cavity by perforating the chest-wall, the lungs collapse. The force with which the lungs are normally trying to collapse amounts to 6 mm. Hg, so we say that in the pleural cavity there is normally a negative pressure of −6 mm. Hg.

As the chest expands in inspiration, it drags the lungs still more open. As these become more distended, their tendency to collapse becomes greater, and hence the negative pressure in the pleura may be increased during forcible inspiration to −30 mm. Hg.

It must be remembered that the heart and great veins and arteries are in the thorax only separated from the pleural cavity by a thin, yielding membrane, so that they are practically exposed to any pressure, positive or negative, which may exist in the pleural cavity.

Hence even at the end of expiration the heart and large vessels are subjected to a negative pressure of −6 mm. Hg. Outside the thorax all the vessels are exposed to a positive pressure, conditioned in the neck by the elasticity of the tissues, and in the abdomen by the contractions of the diaphragm and abdominal muscles.

Now blood, like any other fluid, will always flow from a point of higher to a point of lower pressure. There must thus be a constant aspiration of blood from peripheral parts into the thorax. This aspiratory force will however not influence arteries and veins alike. The arteries, having thick comparatively non-distensible walls, will be very little affected by the negative pressure obtaining in the thoracic cavity, whereas the thin-walled distensible veins will be very largely influenced by the same factor. The total result then of the negative pressure in the pleural cavities is to increase the flow of blood from the veins into the heart, without affecting to any appreciable degree the outflow of blood from the heart into the arteries. The more pronounced the negative pressure in the thorax, the greater will be the amount of blood sucked into the heart from the veins. During inspiration therefore, the heart will be better supplied with blood than during expiration, and this factor in itself will tend to raise the arterial blood pressure.

The inspiratory descent of the diaphragm will moreover tend to increase the inflow into the heart by raising the positive pressure in the abdomen, so that blood is *pressed* out of the abdominal veins and *sucked* into the heart and thoracic veins.

Still more important is the influence of the respiratory movements on the circulation through the lungs. In trying to understand this influence, it must be remembered that the pulmonary capillaries lie in a certain amount of elastic and connective tissue, and are separated on the one side by the alveolar epithelium from air at the ordinary atmospheric pressure, and on the other by the pleural endothelium from the pleural cavity, where the pressure varies from 6 to 30 mm. Hg below the atmospheric pressure. We may therefore consider the pulmonary capillaries as lying between, and attached to, two concentric elastic bags, as represented in Fig. 202. Under normal conditions, since these bags are always tending to collapse, the inner one must be pulling away from the outer one, and the outer one from the chest-wall. Hence there must be a negative pressure in the tissues between these two bags—a negative pressure which in the expiratory condition will be something between 0 and – 6 mm. Hg, and in the inspiratory condition between 0 and – 30 mm. Hg. If we regard the average pressure within the pulmonary capillaries as constant, these capillaries must be more dilated in the inspiratory than in the expiratory condition, as shown in the diagram (Fig. 203). Now this dilatation of the pulmonary capillaries will have two effects. Their capacity will be increased and the resistance they present to the flow of blood will be diminished.

Let us now consider what effect these changes will have on the general arterial blood-pressure. We will assume that during expiration (Fig. 202) the pulmonary vessels have a capacity of 25 c.c., and that the beat of the right heart is forcing through them 10 c.c. of blood per second. So long as the chest remains in the expiratory condition, 10 c.c. of blood will be flowing into the left heart and into the aorta, so that the systemic blood-pressure will remain constant. Now let us suppose that an inspiratory enlargement of the thorax takes place (Fig. 203). The negative pressure in the pleura is increased, the two walls of the lung are pulled farther away from one another, and there is a general enlargement of the pulmonary capillaries. We will assume that this enlargement increases the capacity of the pulmonary capillaries from 25 to 30 c.c. Owing to this increased capacity, the first 5 c.c. of blood, which flows into the lungs after the beginning of inspiration, will not flow out through the pulmonary vein, but will simply serve to bring the capillaries into the same state of distension as before. Hence at the beginning of inspiration the flow through the pulmonary vein will be diminished; there will be less blood discharged into the left heart, and therefore a fall in systemic pressure. As soon however as the increased capacity of the pulmonary vessels is made up, the dilating effect of the inspiratory movement of these vessels will aid the flow through the lungs, in consequence of the diminution of resistance, so that the same force of the right

FIG 202

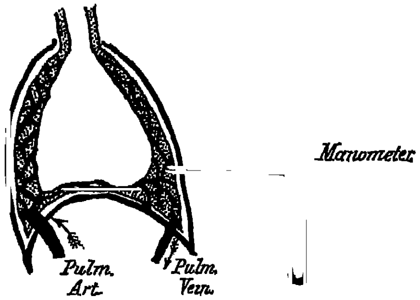


Diagram to show condition of pulmonary vessels in expiration

FIG. 203

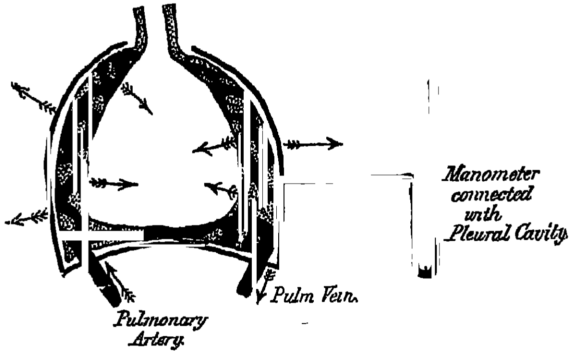


Diagram to show condition of pulmonary vessels in inspiration heart, which drove 10 c.c. of blood per second through the former resistance during expiration, will now drive more, say 12 c.c. of blood. There is thus more blood entering the left heart, and therefore a rise of systemic pressure during the last three quarters of the inspiratory movement.

Expiration will have exactly the reverse effect. At the beginning of expiration there is a diminution of capacity in the pulmonary vessels from 30 to 25 c.c. Hence during the first second of expiration the outflow of blood from the pulmonary vein into the left heart will be 17 c.c. (12 c.c. + 5 c.c.). After this, the increased resistance in the pulmonary capillaries in consequence of their constriction will come into play, and the flow of blood through them will fall once more from 12 c.c. to 10 c.c. Hence at the beginning of expiration the inflow of blood from the pulmonary vein into the left heart is greater than at any period. The arterial pressure will therefore rise to its greatest height at the beginning of expiration, and will fall during the last three quarters of expiration, but will attain its minimum only at the beginning of the next inspiration.

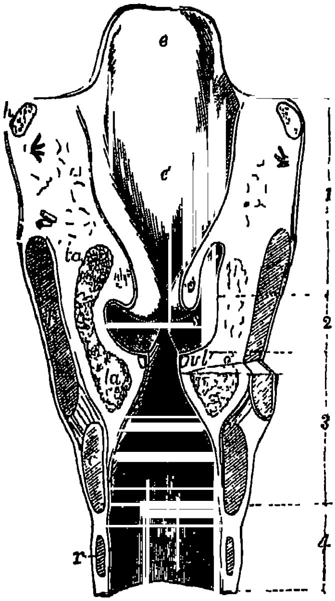
In this way the effect of the respiratory movements on the systemic blood-pressure can be entirely explained by the influence they exert on the lung vessels or lesser circulation.

SECTION 5

VOICE AND SPEECH

Voice.—The voice is produced by an expiratory blast of air being forced through the narrow interval between the true vocal cords. These, which are thin, membranous, and elastic, are set into vibration by the current of air, and the vibrations are communicated in turn to the air in the upper air-passages. The pitch of the sound produced depends on the rapidity of vibration of the vocal cords.

FIG 204



Anterior half of the larynx, seen from behind The section on the right side is somewhat in front of the left side *e*, epiglottis; *e'*, cushion of epiglottis, *t*, thyroid cartilage, *s*, *s'*, ventricle of larynx; *h*, great cornu of hyoid bone; *t a*, thyro-arytænoid muscle; *v l*, vocal cords Above the ventricles are the false vocal cords *r*, first ring of trachea (A Thomson)

The vocal cords are composed of elastic and muscular fibres, covered over by mucous membrane, and running from the anterior processes of the arytænoid cartilages behind to the posterior surface of the angle of the thyroid cartilage in front The arytænoid cartilages are small pyramidal masses of fibro-cartilage resting on the back part of a ring-shaped cartilage, the cricoid cartilage This is thin in front, but thick behind, being produced upwards at its back part for the attachment of the arytænoids

The thyroid cartilage consists of two wings or alæ, articulated to the sides of the cricoid, so that the back part of the cricoid can move backwards and forwards

These four cartilages form the skeleton of the larynx By their relative positions the tension of the vocal cords and the shape of the rima glottidis are determined. These movements are carried out by the following muscles

The *crico-thyroid* muscle passes downwards and forwards from the lower part of the thyroid cartilage to the front part of the cricoid

The *posterior crico-arytænoid* muscle arises from the posterior surface of the cricoid cartilage and is inserted into the outer angle of the arytænoid cartilage

FIG 205

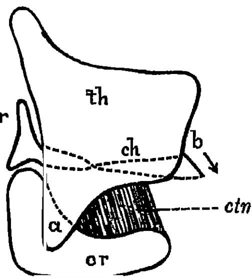


FIG 206

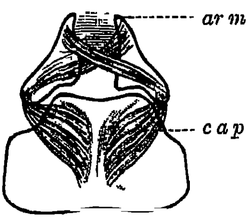


FIG 206 —Side view of cartilages of larynx *th*, thyroid cartilage, *ar*, arytænoid cartilage, *cr*, cricoid cartilage, *ctm*, crico-thyroid muscle, *ch*, vocal cords

FIG 207 —Back view of larynx. *ar m* arytænoid muscle with the oblique fibres which pass round to join the arytæno-epiglottidean muscles, *c a p* posterior crico-arytænoid muscles.

The *lateral crico-arytænoid* runs upwards and backwards from the middle third of the upper border of the cricoid cartilage to the anterior margin of the base of the arytænoid cartilage

The *arytænoid* is a single flat muscle running horizontally between the posterior borders of the two arytænoid cartilages

The *thyro-arytænoid* muscles run from the internal surface of the thyroid cartilage, close to the angle, backwards, to be inserted into the lateral border of the arytænoid cartilage, the most internal fibres being contained in the vocal cords, and inserted into the processus vocalis of the arytænoid.

The false vocal cords are two ridges of mucous membrane, lying over and parallel to the true vocal cords, and separated from them by a lateral recess known as the ventricle of the larynx

During ordinary respiration the glottis or opening between the vocal cords remains about half open, being rhythmically widened with every inspiration. For the production of voice, the free borders of the vocal cords must be brought so near to one another that they almost touch, and a narrow chink with parallel sides is formed. At the same time they must be more or less tense, according to the pitch of the note to be produced. Both these changes are effected by the agency of muscles, the narrowing of the glottis by the contraction of the lateral crico-arytænoid muscles acting in conjunction with the posterior arytænoid and the external thyro-arytænoid muscles. The tightening is brought about by the contraction of the crico-thyroid. This muscle raises the anterior part of the cricoid cartilage so that its upper part, to which the arytænoids are attached, is carried backwards, and thus the vocal cords are put on the stretch. At the same time the tension may be regulated by the contraction of the internal thyro-arytænoid muscles.

The pitch of the tone depends on—

1. The length of the vocal cords. It is well known that the pitch of a stretched string varies inversely as its length. A piece of catgut one foot long will, on being struck, give a note an octave higher than a similar piece two feet long, if both are under the same tension. Comparative measurements show that the vocal cords of men are one and a half times the length of those of women, and this explains the difference in the pitch of their voices. Among men those with a tenor voice have shorter vocal cords than those with a bass one.

2. Tension of the vocal cords, which is modulated by the degree of contraction of the crico-thyroid muscle.

The intensity or loudness of the voice depends on the strength of the expiratory blast of air, since the more powerful this the greater the amplitude of the vibrations of the vocal cords produced.

The changes in the glottis accompanying phonation are best studied with the aid of the laryngoscope This consists essentially of two mirrors, the larger, which has a small hole in the middle, is fastened on to a spectacle frame, which the observer wears This mirror is used to reflect a powerful light into the back of the pharynx of the person to be observed. A small round mirror about half an inch in diameter, mounted on a handle, is then introduced into the pharynx until it is directly over the opening of the larynx. The observer then sees in the small mirror a reflected image of the epiglottis and arytæno-epiglottidean folds, with the true and false vocal cords lying between them

The human voice extends to about 3½ octaves, although it is rare to find any individual compass extending over two octaves. In men two kinds of voice can be distinguished—the chest register and the head register or falsetto. In the latter form of voice it is said that the vocal cords are wider apart, and that only their innermost margins are set into vibration by the current of air.

Speech.—Articulate speech is produced, not in the larynx, but in the mouth and pharynx. If these parts alone are called into play, the expiratory blast of air is so modified as to give rise to whispering speech ; if at the same time there is a production of voice in the larynx, ordinary speech is the result.

The sounds that take their origin in this way are divided into vowel sounds and consonants.

The *vowels* a, e, i, o, u (pronounced ah, eh, $\overline{\text{ee}}$, o, $\overline{\text{oo}}$) are *tones, i.e.* are produced by a regular series of vibrations.

The special characters of each vowel sound were shown by Helmholtz to be due to the combination of overtones, which is different for each vowel. This was determined in the following way:—A person was made to tone the vowel sounds on one particular note, and by means of resonators the component vibrations of each vowel sound were analysed. These being found, the experiment was completed by reforming the vowel sounds synthetically by means of tuning-forks arranged to vibrate at the same notes as the notes of the resonators that picked out the sounds in the first experiment.

Thus if *b* be taken for the fundamental tone,

$b + b_1 = u(\overline{oo})$

$b + b_1$ (loud) $+ f_2$ (soft) $= o$

$b + b_1$ and f_2 (moderately loud), f_1 (louder), f_3, a_3 and b_3 (loud) $= e$ (eh)

i = $\overline{\textit{ee}}$ could not be reproduced, since its higher overtones could not be artificially represented by means of tuning-forks.

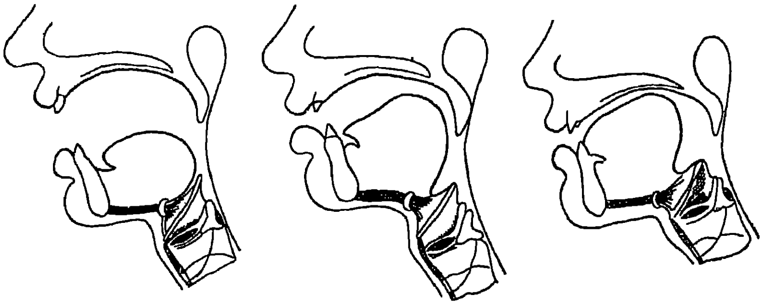
The difference in the overtones accompanying the fundamental tone, and therefore in the vowel sounds, is brought about by changes in the shape of the cavity of the mouth and pharynx (Fig. 207). When *o* and $\overline{\textit{oo}}$ are sounded, the mouth-cavity has the shape of a flask without a neck, the opening being situated at the mouth. The opening is narrow when $\overline{\textit{oo}}$ is sounded, wider with *o*.

When *a* (*ah*) is sounded, the mouth-cavity assumes a wide conical form, the widest part of the cone being at the mouth. With *e* (*eh*) and *i* (*ēē*) the cavity assumes the form of a flask with a long narrow neck which is formed by the raising of the tongue, leaving a narrow canal between this organ and the hard palate.

These changes can be observed roughly by any one on himself if he intones *oo*, and then gradually changes the sound to *o*, *ah*, *e*, *i*, directing close attention to the changes that he is making in his mouth.

The vowel sounds, we may conclude, are brought about by variations in the shape of the cavity of the mouth and pharynx, which alter the quality of the tone produced in the larynx by intensifying some and suppressing other harmonics or overtones.

FIG 207



A (*ah*) *U* (*ōō*) *I* (*ēē*)

Shape of the oral cavity in the production of the vowel sounds, *A*, *U*, *I* (Grützner)

Diphthongs are produced by changing the form of the mouth-cavity from that of one vowel-sound to the other, so that one sound follows directly after the other; thus *ai* = *ah-ee* run together and abbreviated. Consonants are sounds produced by a sudden check being placed in the course of the expiratory blast of air by closure of some part of the pharynx or mouth. They are classified into labials, dentals, or gutturals, according as the check takes place at the lips, between teeth and tongue, or between back of tongue and soft palate.

In the production of *nasal* sounds, such as *m*, *n*, or *ng*, the mechanism is the same as for the production of *b*, *d*, and *g*, except that the posterior opening of the nares is not kept shut by the soft palate, so that part of the sound comes continually through the nasal passages, when it acquires a peculiar resonance. These sounds are on this account often spoken of as *resonants*. The *aspirates* are produced by the passage of a simple blast of air through a narrow opening which may be at the throat as in *h*, between tongue and teeth as in *th*, or between lips and teeth as in *ph* or *f*.

477.

CHAPTER X P. 434-477.

EXCRETION—FUNCTIONS OF THE KIDNEYS AND SKIN

Section 1

THE URINARY CONSTITUENTS AND THEIR ORIGIN IN THE BODY

The consideration of the lungs, which are organs engaged at the same time in absorption and excretion, leads us on naturally to those organs by which the remaining waste products of the organisms are eliminated, *i.e.* the kidneys and skin.

The main work of the kidneys is the excretion of urea, the product of the nitrogenous waste of the body. This is turned out dissolved in water, together with certain other nitrogenous extractives, salts, and water, which together make up the urine.

Human urine in a fresh condition is a clear yellow fluid, with characteristic odour and sour reaction. Its specific gravity is on the average 1016—1020. It is free from organised elements. An average man of 66 kilos weight passes in twenty-four hours about 1,500 grms. of urine. This contains about 73 grms. of solids, which are made up as follows:

1	Urea	33	grms
2	Uric acid	0 5	,,
3	Hippuric acid	0 4	,,
4	Creatinine	0 9	,,
5	Pigment and other substances	10	,,
6	Sulphuric acid	2	,,
7	Phosphoric acid	3	,,
8	Chlorine	7	,,
9	Potassium	2 5	,,
10	Sodium	11	,,
11	Ammonia	0 7	,,
12	Calcium	1	,,
13	Magnesium		

It also contains about 15 volumes per cent. of gas, consisting chiefly of carbon dioxide, with a small amount of nitrogen.

The acidity of the urine is due to the presence of acid sodium phosphate, and is equivalent to about 2 grms. of oxalic acid in twenty-four hours. While active digestion is going on, the urine may be for a while alkaline, owing to the secretion of hydrochloric acid by the stomach. The reaction varies with the nature of the food. In herbivora the urine is normally alkaline, becoming acid only when they have had no food. In this condition their metabolism is going on at the expense of their own bodies, so that they may be regarded as carnivorous for the time being. The acidity of the urine diminishes on standing, and if the fluid be exposed to the air, a development of micro-organisms (*Micrococcus ureæ*) takes place. By their agency the urea is combined with two molecules of water to form ammonium carbonate, and the urine becomes strongly alkaline and ammoniacal.

Urea

Of these constituents, UREA or carbamide is by far the most important, since the greater bulk of the nitrogen produced by the disintegration of proteins leaves the body in the form of urea.

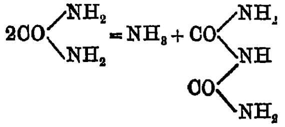
It may be prepared from urine in the following way:—The urine is evaporated to a small bulk ($\frac{1}{6}$), and strong pure nitric acid is added in excess, keeping the mixture cool. Crystals of urea nitrate are deposited. These are collected and dried between filter-paper, and made into a paste with a large quantity of barium carbonate and spirit. The paste is dr water-bath and extracted with alcohol. The alcoholic extract is and allowed to evaporate, when crystals of urea separate out redissolved, decolorised by animal charcoal, and allowed to c more

Urea crystallises in four-sided pris and colourless, readily soluble in a nitric acid it forms nitrate of octahedra (Fig. 208). It also f with oxalic acid (Fig. 209).

On heating, it melts an and forming *biuret*.

make
ena cava,
ffering with
ficult operation
eviously suggested
mber of animals in
formed, the portal vein
was supplied with blood only
In this case the portal blood
eneral circulation before arriving
therefore found that any increase of
such as that caused by a protein

The reaction may be represented as follows:



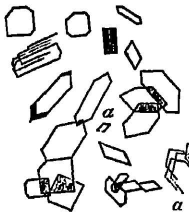
$$2CO\begin{matrix}NH_2\\NH_2\end{matrix} = NH_3 + CO\begin{matrix}NH_2\\NH\\\end{matrix} \quad CO\begin{matrix}NH\\NH_2\end{matrix}$$

On further heating cyanuric acid $C_3H_3N_3O_3$ is formed.

Urea may be formed from ammonium cyanate, with which it is isomeric, by simply heating with water.

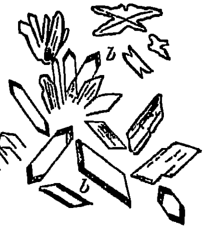
On exposure to the air urine becomes strongly alkaline, and smells of ammonia. At the same time the earthy phosphates are precipitated. This change (which may be prevented by boiling the urine in a flask, the neck of which is closed by cotton wool) is due to infection of the urine by a micro-organism, *Micrococcus ureæ*. Under the influence of this organism the urea undergoes hydration, taking up two molecules of water and being converted into ammonium carbonate.

FIG 208.

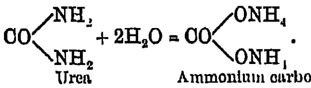


Urea nitrate.

FIG 209.



Urea oxalate.



$$CO\begin{matrix}NH_2\\NH_2\end{matrix} + 2H_2O = CO\begin{matrix}ONH_4\\ONH_4\end{matrix}.$$

Urea Ammonium carbonate

nt with an alkaline hypobromite it is de-
formation of free nitrogen and carbon

$$= CO_2 + N_2 + 3NaBr + 2H_2O.$$

vantage of in the quantitative
urine are treated in a closed
line sodium hypobromite
lved by the excess of alkali
in a graduated cylinder

over water. From the amount of nitrogen given off, the amount of urea present in the urine may be calculated. 35·4 c.c. of nitrogen correspond to 1 decigram of urea.

Since urea is the end-product of the metabolism of the proteins taken in with the food, whether these have been built up to form constituent parts of the living cells of the organism or have been broken down at once on their entry into the body, the amount of it excreted in the day is an index to the activity of the protein metabolism. Hence it is increased by a large protein diet; as well as under conditions such as fevers, when a rapid disintegration of the tissues is going on. It is moreover increased by administration of nitrogenous extractives, such as glycine or leucine, or of combinations of ammonia with carbon dioxide or vegetable acids, or of large quantities of water.

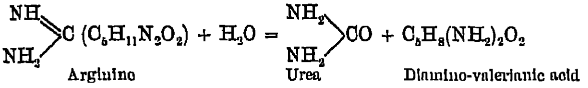
Origin of Urea

The
Urea is not formed in the kidneys. If the kidne ammonia
animal be extirpated, urea accumulates in all the ti ious sub-
organs of the body, in which it is found at de
quantities. Circulating blood constantly cont the li r pre-
proportion of urea, and the kidney-cells mere Sinc a sl the
urea and turn it out into the urinary tubule roug ke up this
inquire what are the immediate precurs So we have to
ors of urea, and in
what organ or organs their transmuta ion into this body is
effected.

Some clue in our investigation of this question is furnished by the results obtained in the experiments on the disintegration of proteins described in Chapter II. We saw there that a protein, on hydrolytic dissociation, broke up into a large number of bodies, belonging to the following classes:

1. Amino-acids, such as leucine, tyrosine, aspartic and glutamic acids.
2. Ammonia.
3. Diamino-acids and bases, such as lysine, arginine, and histidine.

We have to inquire whether any of these or allied substances occur as stages in the normal metabolic processes of the body and by what chemical processes they are converted into the end-product, urea. In the case of one of these bodies, arginine, the derivation of urea is extremely simple, since mere boiling with baryta water serves to split off part of the molecule in the form of urea, according to the following equation:

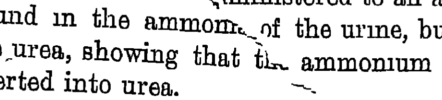


$$\begin{matrix}NH_2\\NH_2\end{matrix}\!>\!C\,(C_5H_{11}N_2O_2) + H_2O = \begin{matrix}NH_2\\NH_2\end{matrix}\!>\!CO + C_5H_8(NH_2)_2O_2$$

Arginine — Urea — Diamino-valerianic acid

This mode of origin will however account at the most only for one-ninth of the total protein. The other eight-ninths of the urea must be obtained from the other decomposition products, especially from the amino-acids. Amino-acids are known to be formed in the intestine in the pancreatic digestion of proteins, and are also formed in the ordinary metabolic processes of the body. We may instance glycine and taurine, which are manufactured by the liver and are combined with cholalic acid to form the bile acids. It is impossible however to conceive chemically the direct conversion of these amino-acids into urea. These bodies all contain[illegible] much larger proportion of carbon to nitrogen than [illegible]nd we must therefore assume that the first stage [illegible] is one of oxidation. The carbon-holding part the m[illegible]e is oxidised to CO_2, and part of this CO_2 unites with [illegible] ammonia of the amino-radical to form ammonium car[illegible]te, from which, by a simple process of dehydration, carba[illegible]de or urea may be formed.

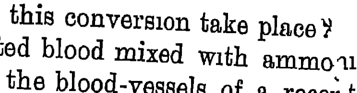
(1)



$$2\begin{matrix}CH_2NH_2\\|\\COOH\end{matrix} + 3O_2 = CO\begin{matrix}\diagup ONH_4\\ \diagdown ONH_4\end{matrix} + 3CO_2 + H_2O.$$

Glycine — Ammonium carbonate

(2)



$$CO\begin{matrix}\diagup ONH_4\\ \diagdown ONH_4\end{matrix} - 2H_2O = CO\begin{matrix}\diagup NH_2\\ \diagdown NH_2\end{matrix}.$$

Carbamide or urea

If ammonium carbonate be administered to an animal, no increase is found in the ammonia of the urine, but a large increase in the urea, showing that the ammonium carbonate has been converted into urea.

Where does this conversion take place?

If defibrinated blood mixed with ammonium carbonate be passed through the blood-vessels of a recently excised mammalian liver, the urea in the blood is found to be increased 200 or 300 per cent., and there is a corresponding decrease in the amount of ammonium carbonate in the blood. The same result, viz. a formation of urea, is obtained if amino-acids, such as leucine or glycine, be added to the blood that is perfused through the liver. We see therefore that the liver has the power of carrying out the series of oxidations and dehydrations described in the previous paragraphs, which result in the formation of urea.

Many experimental facts point to the conclusion that this power is normally exercised during life, and is indeed one of the chief functions of the liver. Comparative analyses of the blood of the portal vein and of the carotid artery or hepatic vein show a marked difference in the ammonia content of the blood Whereas carotid blood contains only 2–3 mg. of NH_3 in 100 c.c., portal blood contains 4–6 or during digestion even 8 mg per 100 c.c. If by any means the proportion of ammonia in carotid blood is raised to that in portal blood, the animal shows symptoms of poisoning, being affected with convulsions or coma, which may end in death. The liver therefore is constantly engaged in removing ammonia from the blood and converting it into an innocuous substance (urea).

The decisive experiment of extirpation of the liver presents in mammals considerable difficulties. Since all the blood from the alimentary canal passes through the liver, extirpation of this organ involves enormous venous congestion of all the portal area. The wall of the intestines becomes thickened and black from effused blood, the blood in the general circulation becomes concentrated and the animal dies within a few hours. It is evident that this difficulty might be overcome if we could in any way make an opening between the portal vein and inferior vena cava, so that the liver might be excised without interfering with the circulation through the gut. This difficult operation has been carried out by Pawlow, though previously suggested by Eck, a Russian surgeon. In a number of animals in which this operation had been performed, the portal vein was ligatured so that the liver was supplied with blood only through the hepatic artery. In this case the portal blood had to pass through the general circulation before arriving at the liver, and it was therefore found that any increase of nitrogenous metabolism, such as that caused by a protein meal, brought about symptoms of *ammoniæmia*, the convulsions and coma mentioned above. On a farinaceous diet, the animals (dogs) could be kept alive a considerable time, and it was observed that the dogs themselves soon recognised the evil effects of a meat diet and changed their tastes in consequence. In animals suffering from these symptoms, the urea in the urine was somewhat diminished, its place being taken by ammonia. A large proportion of this substance was present in the form of ammonium *carbamate*. This fact points to the possibility that the combination of ammonia and carbon dioxide in the tissues results in the formation of this salt rather than of the carbonate, and that the ammonium carbamate is therefore the immediate precursor of urea. In dogs with an Eck's fistula and the portal vein ligatured, obstruction of the hepatic artery brings about death within twelve to twenty-four hours. During this time a small amount of urine may be secreted, containing a fair proportion of urea, a fact which has been interpreted as showing that other tissues besides the liver take part in the formation of urea.

The importance of the liver for the transformation of the amino-acids is illustrated by the fact that in acute yellow atrophy of the liver, as well as in the similar condition brought about by the administration of phosphorus, the urea may disappear from the urine, its place being taken by leucine, tyrosine, and other amino-acids, as well as ammonia.

Confirmatory evidence on this subject is furnished by experiments on birds. In this class there is no need to perform Eck's fistula, since there is normally a communication (the vein of Jacobson) between the portal vein and the renal veins, and so with the vena cava (Fig. 210). Hence they may survive the operation of extirpation of the liver for several days, during which time the kidneys continue to perform their normal functions. Unfortunately for our present question, in birds the greater part of the nitrogen is excreted as uric acid, and not as urea Extirpation of the liver causes an almost total disappearance of the uric acid in the urine, and a corresponding appearance of ammonia In healthy geese, for instance, the nitrogen eliminated as uric acid amounts to from 60 to 70 per cent., and as ammonia to from 9 to 18 per cent. of the total nitrogen.

After removal of the liver the uric acid nitrogen represents only 3 to 6 per cent., and the ammonia 50 to 60 per cent. These figures show clearly that in birds ammonia is a precursor of uric acid, and that the presence of the liver is essential for its conversion into this substance.

It is interesting to notice that under such conditions a large quantity of lactic acid occurs in the urine combined with the ammonia as ammonium lactate—a fact not without significance in view of the artificial synthesis of uric acid from trichlorlactic acid and urea.

FIG 210.

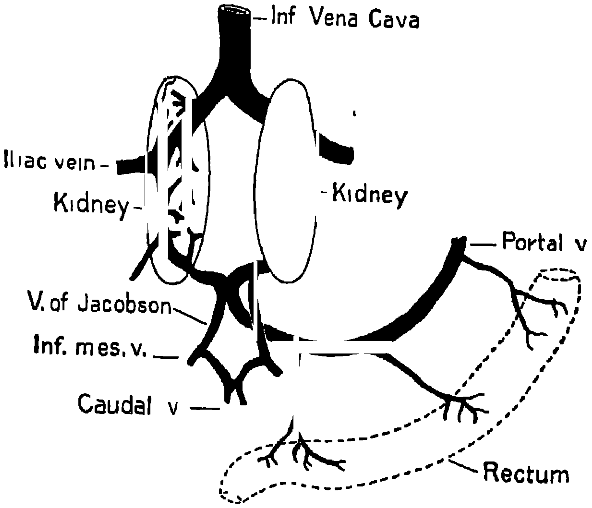
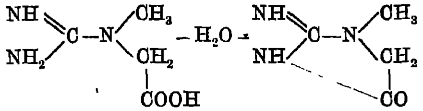


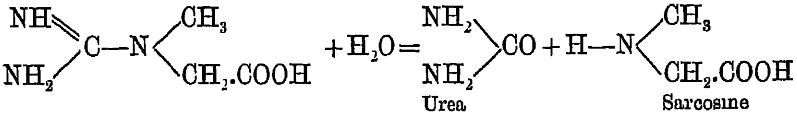
Diagram to show the arrangement of the veins in the bird, with the communication of the renal and portal veins (After Moiat)

Another important precursor of urea is represented by *creatine*. This nitrogenous substance occurs in the organism in far larger quantities than any other extractive. The body of a normal-sized man contains about 90 grms., chiefly in the muscles.

Creatine can be prepared by treating Liebig's extract of meat with baryta water to precipitate phosphates, removing the excess of baryta with CO_2, and then concentrating the filtrate on a water-bath to a thick syrup. In a few days a crystalline deposit of creatine is formed. The crystals are transparent colourless prisms, soluble in water, almost insoluble in absolute alcohol. On heating with dilute mineral acids creatine loses a molecule of water and is converted into creatinine Thus



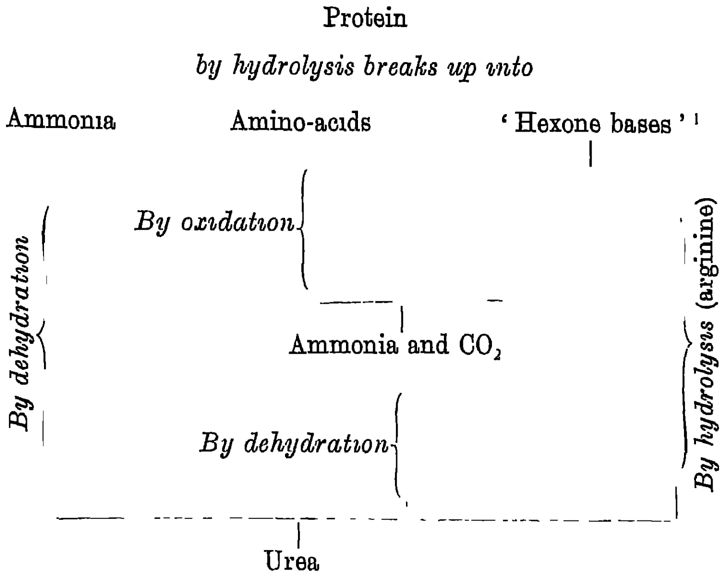
On boiling creatine with baryta water it is split up into urea and sarcosine—an amino-acid, according to the following equation:



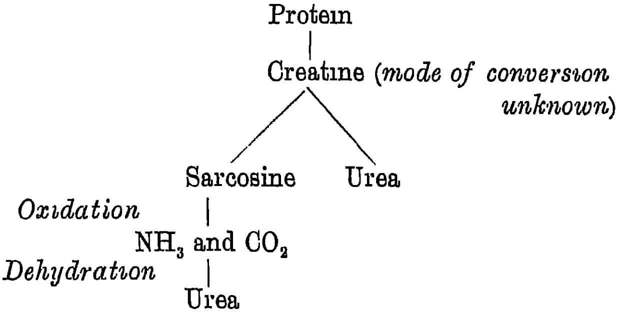
and it is conceivable that a similar decomposition takes place in the muscles, the sarcosine passing on to the liver, and there being converted into ammonium carbonate and then into urea. The following fact seems at first against this view Creatine taken with the food or injected into the blood calls forth no increase of urea in the urine, the whole quantity being excreted in the urine as creatine or creatinine. We must conclude from this experiment that the creatine does not leave the muscle as such, but that it is broken down in the muscle into urea and an amino-acid, or still further oxidised into ammonia and carbonic acid, which are then turned out into the lymph and blood-stream.

Direct experiments by Schöndorff seem to point to a formation of ammonia in muscles during activity, and we know that CO_2 is the most prominent product of muscular metabolism. But in these experiments, which consisted in the estimation of the ammonia in defibrinated blood before and after passage through the vessels of a hind limb, the muscles of which were tetanised through the nerve, there was also an increased formation of lactic acid It is therefore possible that the ammonia was the direct result of the production of acid and therefore only indirectly due to the state of activity of the muscle We do not yet know whether lactic acid is produced in contraction of a muscle under absolutely normal conditions, and therefore cannot regard Schondorff's experiments as absolute proof of the formation of ammonia under such normal conditions

The various stages in the formation of urea from protein may be roughly represented by the following schema·



Alternative process?



---

[1] Nothing is known as to the fate of these substances in the body, though it is highly probable that they, as well as the residue left after the hydrolysis of arginine, undergo changes similar to those which have been proved to take place in the case of the simple amino-acids.

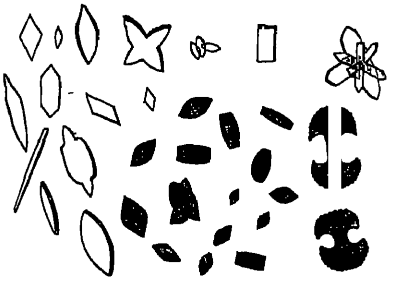
Uric Acid

URIC ACID ($C_5H_4N_4O_3$), which occurs constantly in the urine in small quantities, is a weak dibasic acid. It is almost insoluble in cold water—a little more soluble in hot water. It is easily soluble in alkaline solutions and in solutions of the alkaline phosphates. In solutions of the latter salts a chemical change takes place, the uric acid withdrawing a part of the alkali from the phosphate to form an acid urate of the alkali, which is more soluble in water than uric acid. Thus:

$$Na_2HPO_4 + C_5H_4N_4O_3 = NaH_2PO_4 + NaC_5H_3N_4O_3.$$

The acid reaction of the urine is due to the presence of the acid sodium phosphate. If the urine be allowed to cool, it is often found that crystals of uric acid separate out, and the urine becomes less acid or even alkaline. This is due to the fact that in cooling the mass-influence of the uric acid is diminished. The phosphoric acid of the phosphate combines with the soda of some of the acid sodium urate, forming disodium phosphate and setting free uric acid, which is precipitated. If the urine be warmed again to the temperature of the body, the converse reaction takes place, acid sodium urate and acid sodium phosphate being formed, and the uric acid is dissolved

FIG 211.



Various forms of uric acid crystals (Frey)

It may be prepared from urine by adding 5 c.c. of hydrochloric acid to 200 c.c. of urine, and allowing the mixture to stand for twenty-four hours. Crystals of uric acid then separate out (Fig. 211). These are generally coloured dark red and form rhombic prisms. The red colour of the crystals is due to the fact that they carry down with them part of the pigment of the urine. If the urine is concentrated, there is very often a brick-coloured precipitate produced on cooling, which dissolves up again if the urine be warmed. This is spoken of as the 'lateritious' deposit, and consists of the mixed urates of potassium, sodium, calcium, and ammonium.

Three classes of urates are described. Taking $H_2\bar{U}$ to stand for uric acid, the salts would be represented as $M_2\bar{U}$ (normal urates), $HM\bar{U}$ (acid urates or biurates), and $HM\bar{U}\ H_2\bar{U}$, or quadriurates. The biurates are the only stable compounds. The normal urates, which are the most soluble, form strongly alkaline solutions The quadriurates are supposed to form the greater part of the urates of urine, but split up spontaneously into biurates and uric acid It is doubtful whether the bodies described under this name are anything more than mixtures of biurates and uric acid

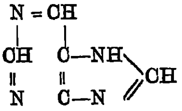
Tests for uric acid.—A few crystals of uric acid are warmed with a little concentrated nitric acid in a porcelain capsule until the nitric acid is evaporated. On adding a drop of ammonia to the yellow residue, a brilliant purple colour is produced (murexide). If potassium or sodium hydrate be used the colour is blue.

Another method is to dissolve the substance in sodium carbonate solution and to place a drop on filter paper previously moistened with silver nitrate. If uric acid is present a yellow or black coloration is produced, due to the reduction of the silver salt. This is known as Schiff's test.

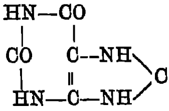
Quantitative determination.—Hopkins' method for the estimation of uric acid is founded on the fact that saturation of a fluid containing uric acid or urates with ammonium chloride causes complete separation of all the uric acid present in the form of ammonium urate. In applying this method the urine is saturated with crystals of ammonium chloride, and a few drops of strong ammonia solution are added. The precipitate of ammonium urate which forms is collected on a filter, washed into a beaker, and boiled with dilute hydrochloric acid The urates are broken up, and the uric acid thus set free is deposited in a crystalline form on cooling. The precipitate of uric acid is collected on a weighed filter, dried, and weighed.

Chemical Relationships of Uric Acid.—A knowledge of the chemical relationships of uric acid is a necessary preliminary to any investigation of its mode of origin in the body We have already seen that it is a member of the group of *purine* bodies

The formula of purine being



that of uric acid is

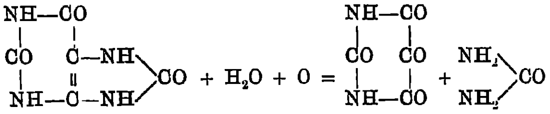


(*i e.* trioxypurine)

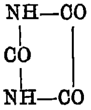
It is apparent from this formula that uric acid consists of a central three carbon chain to which are attached two urea groups, and it is easy to understand the synthesis of uric acid by fusing together trichlorlactic acid or trichlorlactamide and urea

Under the action of oxidising agents one or both of the urea groups is split off

Thus nitric acid splits off the right-hand group, forming urea and a body known as alloxan

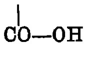


Further oxidation converts the alloxan into parabanic acid



and CO_2,

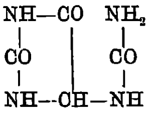
and parabanic acid by hydrolysis is finally converted into oxalic acid



$$\begin{array}{l} CO-OH \\ | \\ CO-OH \end{array}$$

and urea

Potassium permanganate on the other hand attacks the central three carbon chain at once, forming allantoin



and CO_2

From the allantoin by processes of oxidation and hydration both urea groups may be split off as before.

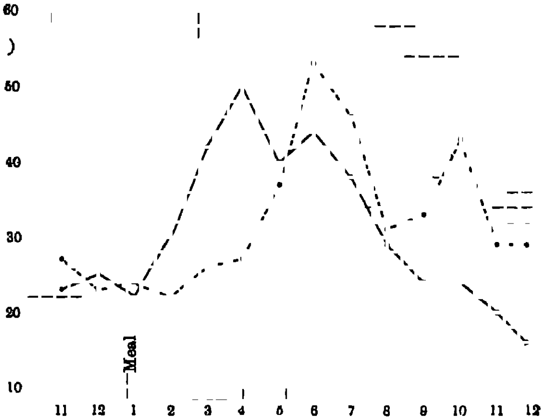
Origin of Uric Acid

We have already seen that in birds uric acid is formed mainly in the liver from ammonia and probably lactic acid. In this class the administration of amino-acids, ammonia, or urea gives rise in every case to increased output of uric acid, and we have reason to believe that the greater part of the transformation is effected by the liver. These results however are no guide to the question of the origin of uric acid in mammals, where this substance forms only a very small proportion of the total nitrogen output.

The first question we have to decide is whether uric acid is a by-product in the ordinary processes of nitrogenous metabolism or whether it is formed along special lines from certain precursors contained in the food. If the former were the case, we should expect to find a constant ratio between the uric acid and the urea in the urine. Although on a constant diet such a ratio does exist (average about 1 to 50), the ratio is at once upset by certain alterations in the character of the food. Thus the uric acid output is very small on a farinaceous diet, and is very little affected by adding to such a diet a large amount of protein in the form of white of egg. A (relatively) large increase is at once observed if a full meal of meat be taken, and a still greater rise is produced by the ingestion of foodstuffs rich in cells, such as sweetbreads (thymus or testis) or liver. The rise of uric acid output following such a meal is very rapid, and precedes the normal post-prandial increase of urea (Fig. 212, p. 448).

This connection of uric acid excretion with the ingestion of cellular organs at once suggests a possible mode of origin for the uric acid. We have already seen that the main constituents of undifferentiated cells, as of their nuclei, belong to the class of nucleo-proteins and nucleins, and that these, on hydrolytic dissociation, give rise to a series of bases, xanthine, hypoxanthine, adenine, belonging to the purine group, *i.e.* to the same class of bodies as uric acid itself. We have at present no adequate evidence as to the effect of the administration of these bases on the output of uric acid in man. It seems probable however that part of the basic residue of nucleo-proteins may undergo oxidation in the body and appear in the urine as uric acid, while another part may avoid oxidation and appear as other less oxidised members of the group, the so-called alloxuric bases of the urine. The nucleo-proteins which give rise to the uric acid may be contained in the food, or be produced in the disintegration of the nuclei, etc., of the tissues of the body itself. Corresponding to these two origins we may distinguish the *exogenous* uric acid, dependent on the food, and an *endogenous* moiety arising from the metabolism of the tissues. As to the organ in which the formation of uric acid is carried on, we have very little evidence. It has been found however that, whereas extract of fresh spleen contains a fair proportion of xanthine, the passage of oxygen through the splenic pulp for some hours causes a conversion of this xanthine into uric acid.

FIG. 212.



Curves showing the hourly excretion of uric acid and urea after a single meal (Hopkins) The continuous line = uric acid output; the dotted line = urea output

The only disease in which there is a large increase in the output of uric acid is leuchæmia, which is generally associated with enlarged spleen and augmentation of the number of leucocytes in the blood Since the post-prandial rise of uric acid is also often associated with a certain amount of leucocytosis, it has been suggested by Horbaczewsky that the uric acid is a special product of the metabolism of the leucocytes Other observers have however failed to detect a parallelism between the number of leucocytes and the uric acid secretion under all conditions

The deposition of sodium urate in the joints, which occurs in gout, seems to be due to a deficient excretion rather than to an increased formation of this substance The whole question is however extremely involved and in need of further evidence with regard to the origin and significance of uric acid in the normal organism

In dogs the administration of uric acid or of hypoxanthine causes an increased excretion in the urine, not of uric acid but of allantoine Administration of adenine, another purine base, apparently causes no alteration at first in the nitrogenous constituents of the urine The dog however finally dies with suppression of urine, and it is found that the epithelial cells of the renal tubules are desquamating and in many places full of uric acid infarcts It seems evident from these various facts that there is a chapter of purine metabolism in the body, of which at present we possess only a few disconnected pages

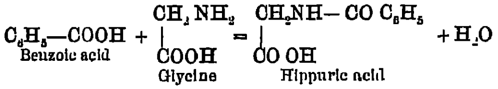
The following table will serve to represent the relation of uric acid to the other xanthine or purine bodies.

Uric acide	$C_5H_4N_4O_3$
Xanthine	$C_5H_4N_4O_2$
Hypoxanthine	$C_5H_4N_4O$
Adenine	$C_5H_5N_5$
Guanine	$C_5H_5N_5O$

Other Nitrogenous Constituents

Creatinine.—The creatinine in the urine is nearly all derived from the creatine contained in the meat that is taken as food.[1] It does not however disappear in hunger, so that a certain amount must arise in the metabolic processes of the body itself. It may be that this quantity merely represents a small percentage of creatine which has escaped further decomposition in the muscles.

Hippuric Acid.—This is only present in small quantities in human urine. The large amount found in the urine of herbivora is due to the fact that in their food are bodies belonging to the aromatic group—the benzoic acid series. If benzoic acid be administered to a man, it is excreted in the urine as hippuric acid, which is a combination of glycine with benzoic acid, with the elimination of a molecule of water:



$$\underset{\text{Benzoic acid}}{C_6H_5{-}COOH} + \underset{\text{Glycine}}{\begin{array}{l}CH_2NH_2\\ |\\ COOH\end{array}} = \underset{\text{Hippuric acid}}{\begin{array}{l}CH_2NH{-}CO\,C_6H_5\\ |\\ CO\,OH\end{array}} + H_2O$$

This synthesis is effected by the living cells of the kidney. If defibrinated blood containing benzoic acid and glycine be passed through the vessels of the kidney for some time, it will be found that their place has been taken by hippuric acid. In the same way, a small amount of hippuric acid is formed if the kidney be chopped up and mixed with blood containing benzoic acid and glycine. If the kidney cells be first killed by exposure to a temperature of 65°, or to the action of alcohol, no hippuric acid is formed, showing that this synthesis is not effected by a mere ferment action, but is intimately dependent on the life of the cell.

---

[1] According to Folin, however, all the creatinine of the urine is derived from the metabolic processes of the body, any creatine contained in the diet being oxidised, or if in excess, appearing in the urine unaltered as creatine

AMMONIA.—Although this constituent occurs in normal human urine only to the extent of about 0·7 gram *per diem*, it is of considerable importance, since it is a measure of the formation or ingestion of acids by the body. If ammonium chloride be given to a fed rabbit, it reacts with the alkaline carbonates derived from the vegetable food to form ammonium carbonate, and this is converted into urea, and appears as such in the urine. If, on the other hand, ammonium chloride be given to a carnivorous animal, there is no such store of alkali to take up the hydrochloric acid. The salt therefore appears in the urine unchanged.

In the same way if dilute mineral acid be injected into the veins of a dog, the reaction of the blood remains normal, but the excretion of ammonia in the urine is increased in proportion to the acid injected. The tissues defend themselves against the acid intoxication by turning out ammonia, and the ammonia in the urine is therefore increased at the expense of the urea.

This self-protective ammonia formation is less marked in herbivorous animals. In these, when the store of vegetable alkaline salts is used, the acid causes a lowering of the alkalinity of the blood. The carrying power of the blood for carbon dioxide is therefore diminished (fixed acid having taken the place of CO_2 and P_2O_5), and the animal suffers from a retention of CO_2 in all his tissues, giving rise to hyperpnœa and dyspnœa and finally to a condition of coma which may end fatally

An analogous condition occurs in cases of diabetes in man. This 'diabetic coma' has been shown to be associated with the abnormal production of large quantities of oxybutyric and diacetic acids. The alkalinity of the blood as well as its CO_2 contents is decreased, while the ammonia of the urine is largely increased in the vain attempt of the organism to saturate the offending acids.

The Salts of Urine

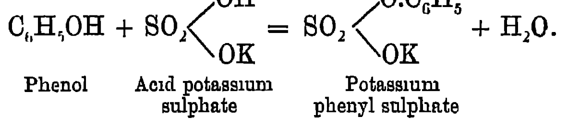
The greater part of the salts of the urine is derived directly from the salts taken in with the food. The combinations of the vegetable acids with alkalies, *e.g.* citrates and tartrates, are oxidised to carbonates, and are in this form eliminated with the urine.

The *phosphates* originate partly from the breaking down of complex phosphorised molecules, such as lecithin, nuclein, and the nucleo-proteins, partly from the phosphates taken in with the food. When the urine becomes alkaline, the calcium and magnesium phosphates are deposited as an amorphous precipitate. If the urine is ammoniacal, ammonio-magnesium phosphate may be formed and precipitated in a crystalline form.

The *sulphur* in the urine arises partly from the sulphates of the food, and partly from protein metabolism. It is found in the urine in three forms :

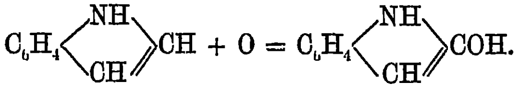
1. Small traces of an unoxidised sulphur compound, allied to cystine.
2. As simple sulphates of the alkalies.
3. As conjugated ethereal or aromatic sulphates.

These latter bodies are important from the fact that they are dependent on putrefactive changes occurring in the intestine, so that their quantity in the urine is an index to the extent of these processes. In the bacterial putrefaction of proteins, bodies of the aromatic series, such as skatol, indol, and phenol, are formed. These, after absorption, unite in the blood-stream with an alkaline sulphate to form conjugated or ethereal sulphates, and as such are excreted by the kidneys. The poisonous aromatic body is thus rendered innocuous.



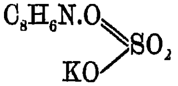
$$\underset{\text{Phenol}}{C_6H_5OH} + \underset{\substack{\text{Acid potassium}\\\text{sulphate}}}{SO_2\Big\langle\begin{matrix}OH\\OK\end{matrix}} = \underset{\substack{\text{Potassium}\\\text{phenyl sulphate}}}{SO_2\Big\langle\begin{matrix}O.C_6H_5\\OK\end{matrix}} + H_2O.$$

Indol and skatol undergo a preliminary oxidation to indoxyl and skatoxyl before the conjugation with sulphuric acid takes place. Thus:



Indol Indoxyl

the indoxyl sulphate of potash having the formula



$$\begin{matrix} C_8H_6N.O \\ KO \end{matrix} \Big> SO_2$$

Indoxyl sulphate of potash is often spoken of as indican, since on oxidation it yields indigo blue If urine containing this body be treated with hydrochloric acid and a drop of chlorine water, a bright-blue colour is produced from the formation of indigo.

Urinary Pigments

An exact knowledge of the pigments of the urine is still wanting. The chief colouring matter is a body known as *urochrome*. The chemical relationships of this body have yet to be discovered. It has no distinctive absorption spectrum. On treating however an alcoholic solution of urochrome with aldehyde, a pigment is produced having an absorption spectrum identical with that of *urobilin*, thus pointing to a common origin of the two bodies. Urobilin itself does not exist in normal urine, which presents no absorption bands. On precipitating normal urine with lead acetate, and extracting the precipitate with acid alcohol, a small trace of urobilin is obtained. Normal urine therefore contains a small amount of a chromogen, which on appropriate treatment may give rise to urobilin. In certain diseases, especially cirrhosis of the liver, the urine may contain large amounts of pre-formed urobilin.

Urobilin free from other pigments may be extracted from urine in the following way:—The urine is saturated with ammonium chloride to throw down urates with the adherent pigment *uroerythrin*, then filtered, acidified, and saturated with ammonium sulphate. This throws down the urobilin, but instead of waiting for the precipitate to form, the urobilin may be dissolved out by shaking the ammonium sulphate solution with a mixture of chloroform (one part) and ether (two parts). The solution thus obtained is yellowish-red, with a well-marked absorption band in the blue end of the spectrum near the Fraunhofer line F.

Urobilin is certainly derived from bile pigment, and therefore indirectly from hæmoglobin. The stercobilin which is formed from bilirubin in the intestines, under the reducing action of putrefaction, is identical with urobilin. Urochrome is probably a product of oxidation of urobilin.

Hydrobilirubin, which is formed by the action of sodium amalgam on bilirubin, presents many similarities to urobilin, with which it was formerly thought to be identical. It contains however about twice the proportion of nitrogen that is contained in urobilin.

1. [illegible]

2. [illegible]

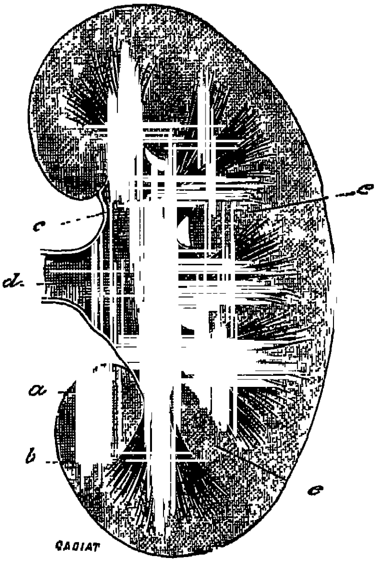
4 [illegible]

SECTION 2

THE SECRETION OF URINE

The kidney may be considered as a compound tubular gland. On cutting into a kidney it is seen to consist of two parts, a granular cortex, and a medullary portion presenting radial striation. The medulla in the human kidney is divided into a number of pyramidal segments, the Malpighian pyramids, each consisting of a number of tubules which open at the apex of the pyramid, the papilla, into the dilated extremity of the duct of the kidney—the ureter. Between the cortex and medulla, in the region known as the boundary zone, are seen a number of large blood-vessels cut across. Small striated prolongations of the medulla stretch up from

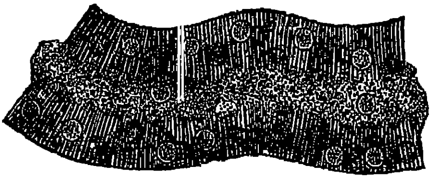
FIG. 218.



Section of human kidney (Cadiat) *a*, cortex; *b*, medulla or Malpighian pyramids; *c*, papilla, *d*, ureter, *e e*, boundary zone the base of the pyramids into the cortex, forming the medullary rays, or pyramids of Ferrein.

The urinary tubule starts in the cortex in a small dilatation—the Malpighian capsule, which is lined by a single layer of flattened cells. Into this capsule projects the glomerulus, a little bunch of capillary blood-vessels, also covered by flattened cells. The capsule leads into the first convoluted tubule, lined with peculiar 'rodded' epithelium. The tubule now becomes much narrower, and dips down into the medullary pyramids as the descending loop of Henle, lined with flattened hyaline epithelium. It then widens as it turns up again, and on reaching the cortex forms the irregular tubule and the second convoluted tubule. These three last-named parts are lined with rodded epithelium. From the second convoluted tubule a junctional tubule leads into the collecting tubule, which is lined with hyaline cylindrical cells. There are thus four different varieties of epithelial cells in the various parts of the tubule, *i.e* scaly cells in the Malpighian capsule, peculiar rodded epithelium in the convoluted and irregular tubules, flattened cells in the descending loop of Henle, and ordinary cylindrical cells in the straight collecting tubes.

Fig 214.



A portion of a convoluted tubule with 'rodded' epithelium (Heidenhain)

There are also certain peculiarities connected with the blood-supply to the kidney. The renal artery breaks up into numerous vessels at the boundary zone between the pyramids and the cortex. From these the straight interlobular arteries pass towards the surface, giving off lateral branches which form the afferent arteries of the neighbouring Malpighian capsules and break up in the glomerulus into a cluster of fine capillaries. These unite again to form the efferent vessel, which is only two-thirds the diameter of the afferent vessel. The efferent vessel leaves the glomerulus and breaks up again into capillaries which supply the walls of the convoluted tubules. Thus the arrangement of the portal system of vessels is repeated in the kidney on a microscopic scale—the vessel taking the blood from the glomerulus breaks up again into a system of capillaries, just as the portal vein does in the liver. The pyramids are supplied by branches of the vasa recta which pass inwards from the arteries in the boundary zone.

Fig. 215

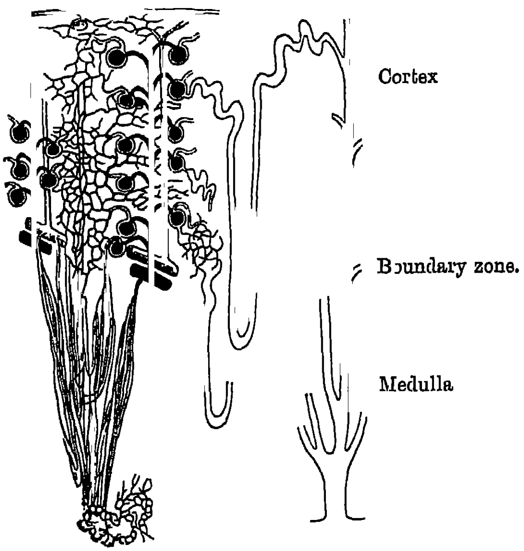


Diagram showing course of urinary tubules, and the distribution of the blood-vessels (from Yeo)

This arrangement of blood-vessels must determine a high pressure in the capillaries of the glomerulus, and a low pressure in the vessels supplying the remaining parts of the tubule. Since these capillaries are covered only by a thin layer of scaly epithelium, it has been thought that filtration plays a great part in the secretion of urine, and that perhaps the fluid parts of the blood are merely filtered off in the capsule, and the useful constituents of the filtrate, together with the excess of water, reabsorbed in the tubules where the pressure in the surrounding capillaries is low. At any rate the histological differences between the glomeruli and tubules indicate that in the secretion of urine we have probably two distinct mechanisms at work, the glomerular and tubular. It will be convenient to deal with these two functions of the kidney separately.

According to the theory just enunciated, the glomerular epithelium acts simply as a filter allowing the water and salts of the blood-plasma to pass into Bowman's capsule. Such a filtration presents no difficulties from a mechanical standpoint. If blood-plasma be filtered through a clay-cell, the composition of the filtrate obtained differs very little from that of the original plasma. If however we make the filtering medium denser by soaking it with gelatin, we find that only the water and salts of the plasma will pass through, the whole of the protein remaining behind. Under these circumstances, a certain limiting pressure is found at which no filtration at all takes place. This pressure, which in the case of blood serum amounts to about 30 mm. Hg, represents the force necessary to effect a separation between the colloid and fluid constituents of the blood-plasma. If the filtration theory be correct, we should expect to find that a certain minimal blood-pressure is necessary for any flow of urine to take place at all, and that when the pressure exceeds this minimum, the rate of secretion will be proportional to the blood-pressure in the glomerular capillaries, or at any rate to the difference of pressure obtaining between the glomerular capillaries and the urinary tubule.

The experimental investigation of this question shows that in many cases at least the urinary secretion follows the mechanical conditions just laid down. If the spinal cord be divided in the neck, the blood-pressure falls to about 40 mm. Hg and the urinary secretion ceases. On the other hand, any procedure which increases the pressure and velocity of the blood in the glomerular capillaries is attended with augmented flow of urine.

The condition of the renal circulation in such experiments is tested by placing the kidney in an oncometer. With free venous outflow, every increase in volume of the kidney denotes increased blood-pressure and blood-flow through that organ.

The parallelism of vascular conditions and urinary flow will be evident from the following table of results.

Procedure	General blood-pressure	Renal vessels	Kidney volume	Urinary flow
Division of spinal cord in neck	Falls to 40 mm.	Relaxed	Shrinks	Ceases
Stimulation of cord	Rises	Constricted	Shrinks	Diminished
Stimulation of cord after section of renal nerves	Rises	Passively dilated	Swells	Increased
Stimulation of renal nerves	Unaffected	Constricted	Shrinks	Diminished
Stimulation of splanchnic nerve	Rises	Constricted	Shrinks	Diminished
Division of one splanchnic nerve.				
a In dog	Unaffected	Dilated	Swells (?)	Increased
b. In rabbit	Falls	Relaxed	Shrinks (?)	Diminished
Plethora . .	Rises	Dilated	Swells	Increased
Hæmorrhage	Falls	Constricted	Shrinks	Diminished

Under all these circumstances, in which the kidney increases in volume, the amount of urine excreted by it is increased. But we have here two factors, either of which may determine an increased flow of urine—1st, increased blood-pressure in the glomerulus ; and 2ndly, increased flow of blood through the kidney. It will be remembered that the flow of lymph from a limb is markedly increased by ligature of the veins ; and this increase is due chiefly to the enormous rise of pressure that takes place in the capillaries, larger than can be brought about by the constriction of the arterioles in other parts of the body. If the secretion of urine were similarly dependent on the intra-capillary blood-pressure, it might be expected that ligature of the renal vein would also cause an increase in the urine excreted. This is not the case. Ligature of the renal vein entirely stops the secretion of urine, and Heidenhain concludes therefore that the glomerular secretion involves the activity of the endothelial cells of the capsule, and is conditioned not by the pressure but by the velocity of the blood through the glomerular capillaries. This operation of ligature of the renal vein is not however a clean experiment. In the first place the small veins of the kidney run alongside of the tubules and when dilated under the influence of venous congestion may press upon the latter, occluding their lumen and so stopping the flow mechanically. Moreover ligature of the renal vein cannot be regarded as equivalent to obstruction of the efferent vessels of the glomeruli. It will be remembered that there is a very great difference as regards the effects on the intestines between ligature of the portal vein and obstruction of the inferior vena cava above the liver. It is impossible to inject the glomerular capillaries either through the renal portal capillaries in the frog or through the renal vein in the mammal, and in view of the presence of well-developed muscular fibres in the vasa afferentia, we have no proof that any given rise of pressure produced in the venous side of the tubular capillaries is transmitted effectively to the glomerular capillaries. It is a common experience to find, in injecting a kidney shortly after the death of the animal, that it is impossible to get any of the injection into the glomerular capillaries, although the injection may flow freely through all the vessels of the medulla.

Fig. 216

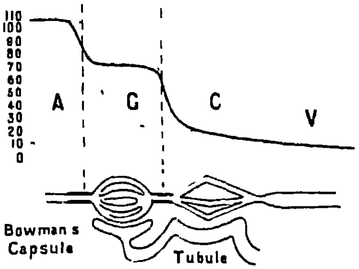


Diagram (after Morat) to illustrate the effect of active changes in the vasa afferentia and efferentia on the pressure in the glomerular capillaries If the vas afferens constricts, the pressure will be represented by the lower dotted line On the other hand, constriction of the vas efferens would raise the pressure in the glomerulus till it almost equalled that in the renal artery, as is shown by the upper dotted line

A, arteries, G, glomerular capillaries, C, tubular capillaries; V vein

The diagram (Fig. 216) will serve to demonstrate the great importance of contraction or dilatation of the muscular fibres of vas afferens or vas efferens for the blood-pressure in the glomerular capillaries, and this factor is one which unfortunately it is impossible to estimate in any experiment.

It stands to reason however that the velocity of the blood must be at least as important as the blood-pressure in the glomeruli. At any given time there is only a small volume of blood in the glomeruli, and if this were not renewed the transudation through the epithelium would concentrate it to such an extent that transudation would be no longer possible under any pressure which the capillaries would stand. In any rapid formation of urine therefore, it is absolutely essential that there should be a rapid renewal of blood in the glomerular capillaries as well as an adequate blood-pressure.

It is interesting to note that, if the renal veins be obstructed for a short time, the urine that is excreted after the removal of the obstruction contains albumen, showing that the short deprivation of oxygen undergone by the cells has injured them, and that they are in consequence no longer able to prevent the passage of the protein constituents of the plasma.

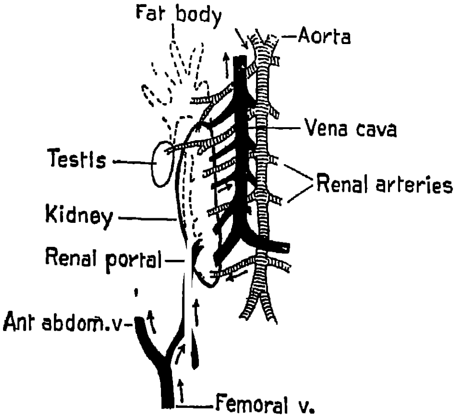
Functions of the tubules.—If we accept the view as to the simple character of the glomerular function (a view that must still be regarded merely as a working hypothesis), we must assume that the glomerular secretion is an almost colourless fluid having the same proportion of salts as the blood-plasma, and like this containing only about 0·05 per cent. of urea. On its way down the tubules this fluid is converted into urine, containing 2 per cent of urea, as well as salts in proportions differing widely from that found in the blood-plasma. What is the nature of the process occurring in the tubules? Is it one of absorption as Ludwig assumed, or is it one of secretion, the specific constituents of the urine being added in large quantity to the watery glomerular fluid? A definite decision between these two theories is not at present possible, although there is no doubt that in its original form Ludwig's theory is untenable. Ludwig ascribed the concentration to processes of diffusion occurring between the fluid in the tubules and the lymph outside the tubules. As a matter of fact if urine and lymph were in contact, separated only by a permeable membrane, the urine would cause a concentration of the lymph, since its osmotic pressure is very much higher than that of the latter fluid. It is difficult to believe however that the whole of the urea of the urine is turned out by a process of filtration in the glomeruli, since, in order to form the 1,500 c.c. of urine containing 30 grammes of urea per day, the glomeruli would have to turn out 60,000 c.c. of urine, of which 58,500 would be reabsorbed by the tubules.

We must see therefore what evidence there is of a secretory function of the tubular epithelium. Older observers described crystals of uric acid in the tubular epithelium of the bird's kidney. In the case of the mammalian kidney it is evidently impossible to trace such a soluble, inert body as urea, and we must have recourse to colouring matters on which the kidney has a special selective activity and which can be detected on their way through the cells. Such a substance is sodium sulphindigotate. If this be injected into the blood-stream, the urine within a minute or two acquires an intense blue colour, although the blood may be only slightly tinged with the dye. If during this period of secretion the animal be killed and its kidney washed through with absolute alcohol in order to fix the dye-stuff, the whole of the kidney is found to be blue, and on microscopic section the only parts free from the dye are the glomeruli. In order to study the seat of excretion of the indigo we must stop the glomerular secretion which carries the blue colour to all parts of the tubule. For this purpose, before the injection, the spinal cord is divided in the neck. The injection then evokes no secretion, but on fixing the kidney in alcohol the cortex alone is found to be blue, and on microscopic section the indigo is found deposited in granules in the lumen and within the striated epithelial cells of the first and second convoluted tubules.

Having thus proved a specific secretory activity of the striated cells of the convoluted tubules with regard to indigo carmine, it is a reasonable assumption to make that these cells exercise a similar function in respect to urea and probably for the other specific constituents of the urine.

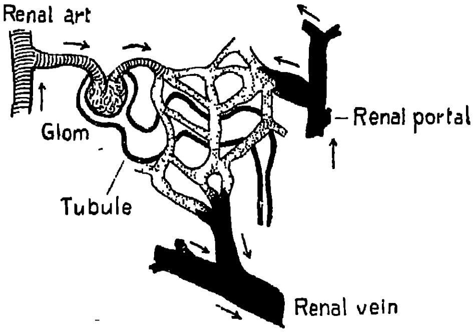
Even if we grant this assumption, it seems necessary to allow also an absorbing function to the tubules. Thus it is found that during the diuresis produced by injection of mixtures of sodium chloride and sulphate, the sulphate is excreted far more completely than the chloride, and this difference is exaggerated if we favour absorption by partial obstruction of the ureter, owing to the greater ease of absorption of the chloride. It is possible that certain parts of the tubules are secretory while other parts are absorptive in function, but we are far as yet from any exact knowledge of the part played by each segment of the tubule in the elaboration of the fully formed secretion.

FIG 217.



The vascular supply to the kidney in the frog

FIG 218



Diagrammatic representation of the course of the blood-flow in the frog's kidney, showing the double blood-supply to the capillaries round the tubules

The ideal method of deciding the relative functions of the glomeruli and tubules would be to collect the secretions of these two parts separately. In the frog and newt, the kidneys have a double blood-supply, the glomerular arteries being branches of the renal artery, whereas the urinary tubules derive their blood partly from the vasa efferentia of the glomeruli, but partly also from a branch of the femoral vein which forms what is called the renal portal system (Figs. 217, 218).

It was shown by Nussbaum that ligature of the renal arteries entirely cut off the circulation through the glomeruli without interfering with the renal-portal circulation, and he stated that, although ligature of the renal arteries stops the urinary secretion, the secretion can be at once induced by injecting a solution of urea into the blood He concluded therefore that the function of the tubules is to secrete urea together with water On the other hand, he states that certain substances, such as sugar and peptone, which are readily excreted by a normal kidney, are not excreted if the renal arteries have been tied, even if a flow of urine be called forth by the simultaneous injection of urea into the blood. It is concluded therefore that sugar and peptone pass into the urine through the glomerular epithelium.

A recent investigation of this subject by Beddard has shown however that, while Nussbaum's anatomical statements are correct, his conclusions are probably fallacious, owing to the absence of control injections of the frogs at the end of the experiment. It is very easy to miss some small vessel going to the glomeruli and then to obtain Nussbaum's results with the injection of urea, but if all the vessels to the glomeruli be ligatured, as proved by a subsequent injection, the secretion of urine ceases absolutely and cannot be evoked by any injection of urea It seems that a certain supply of arterial blood is necessary to the normal life of the tubular epithelium, since this undergoes fatty degeneration and desquamates in consequence of the occlusion of the glomeruli. These experiments have been repeated, an adequate supply of oxygen to the tubular epithelium being provided by keeping the frog in an atmosphere of pure oxygen. Under these conditions the desquamation of the epithelium does not take place, and by injection of urea, a small flow of urine can be induced. This must have been secreted by the tubules.

Regulation of urinary secretion.—In most other glands of the body we have seen that their activity was subject to nervous influences. The submaxillary gland is supplied by secretory nerves, stimulation of which calls forth a flow of saliva independently of any change in the blood-stream. The conditions in the kidney however are different. The function of this organ is to purify the blood of its waste products, and hence it is only necessary that the cells should react to changes in the composition of the blood. If the blood becomes more watery, the excess of water must be turned out into the urine; if it contains too much urea or sugar, these bodies must be excreted, in order that the blood may act as a normal living medium, and not as a poison to the tissues which it traverses. There is indeed no evidence of secretory nerves to the kidney. The urinary secretion is conditioned only by the composition and amount of blood supplied to it. Injection of water or of diuretics, such as sodium acetate or urea, into the blood, causes an expansion of the kidney from dilatation of its vessels, and increased flow of urine, until the blood is restored to its normal composition.

The nervous system can influence this secretion of urine, but only by its action on the vessels. In this way may be explained the copious flow of dilute urine which may occur under the influence of emotions or in hysteria. Increased secretion of urine brought about by the application of cold to the skin may be due to reflex dilatation of the renal blood-vessels.

In the dog the vaso-motor nerves to the kidney pass from the spinal cord chiefly through the anterior roots of the 11th, 12th, and 13th dorsal nerves, and stimulation of the peripheral ends of these roots causes shrinking of the kidney. If slowly repeated rhythmical stimulation instead of the ordinary faradic current be applied to these nerves, swelling of the kidney may be produced, showing that these roots also contain vaso-dilator fibres.

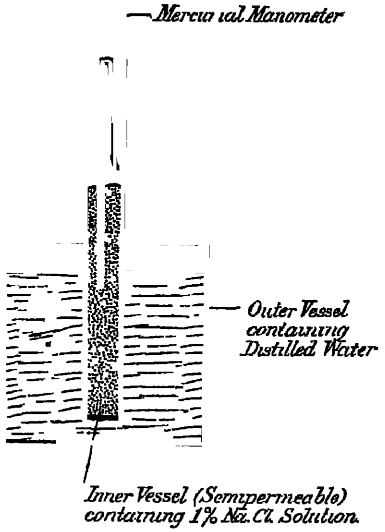
On the Work done by the Kidney

I have already mentioned certain arguments against the hypothesis that the urine is separated from the blood circulating in the kidney by a simple process of filtration. A still stronger argument however is furnished by the fact that we can measure the work done by the kidney in the secretion of urine, and find that it is very much greater than could be accomplished by the pressure of the blood in the renal capillaries.

The measurement of the work done by the kidney depends on a determination of the *osmotic pressures* of the blood-plasma and urine respectively. Before describing these results, it will be necessary to say a few words as to what is meant by the term 'osmotic pressure.'

It is well known that, if a bladder containing strong salt solution be placed in a vessel of distilled water, water passes into the bladder by diffusion or osmosis, so that the bladder swells and becomes tense. A manometer connected with the bladder will show a considerable rise of pressure (osmotic pressure). It is evident however that we cannot expect under these conditions to get the total possible rise of pressure in the bladder; since the salt diffuses out of the bladder while the water is diffusing in, and moreover the animal membrane permits of a distinct filtration, *i.e.* leaks, as soon as the pressure within it has attained a certain height. It is necessary then, in order to measure the osmotic pressure of a solution, to enclose it in some vessel whose walls will only allow of the passage of water, and will not permit salt to pass out either by diffusion or by filtration. Such a vessel may be made by washing out a porous cell, first with copper sulphate and then with potassium ferrocyanide. An insoluble precipitate of copper ferrocyanide is deposited in the pores of the earthenware, and it is found that these now allow only water to pass through, and are perfectly impermeable to dissolved salts. If we arrange such a cell as in the diagram (Fig. 219), fill it with 1 per cent. NaCl solution, and then suspend it in distilled water, we find that water diffuses in until the pressure, as shown by the attached manometer, has attained a great height. The osmotic pressure of a 1 per cent. NaCl solution is equal to about 5,000 mm. Hg. If by artificial means we increase the pressure in the cell above this height, water will be pressed through the semi-permeable walls of the cell, and the solution will become more concentrated. In order then to make a 1 per cent. NaCl solution more concentrated, we must employ a pressure greater than 5,000 mm. Hg.

Fig 219


Mercurial Manometer
Outer Vessel containing Distilled Water
Inner Vessel (Semipermeable) containing 1% Na. Cl. Solution.

Now it is found that the osmotic pressures of various solutions depend, not on the nature of the dissolved substance, but merely on the number of molecules present in solution The osmotic pressure of any solution is in fact equal to the pressure which the dissolved substance would exert if it occupied the same space in the form of a gas.

Hence, if we can determine the osmotic pressures of the blood-plasma and of the urine, we can estimate what work must be done by the kidney cells in order to separate from the blood-plasma a fluid having the osmotic pressure of the urine.

We may take as example an instance quoted by Dreser in which 200 c.c. urine had been secreted. The blood-plasma in this case had an osmotic pressure equal to a 0 92 per cent. NaCl solution. The urine had an osmotic pressure equal to a 4·0 per cent. NaCl solution. It may be shown mathematically that in this case the kidney had performed 37 kilogrammetres of work in the secretion of the 200 c.c. urine. Very interesting is the determination in this way of the maximum force of the kidney. In one case in which a cat had been deprived of water for three days, the urine was so concentrated that it was equivalent to an 8 per cent salt solution. The blood-plasma in the same animal had an osmotic pressure equal to 1·1 per cent. NaCl. The difference of osmotic pressures in this case was equal to 498 metres of water, so that the kidney had separated the urine from the blood against a pressure of 49,800 grams per square centimetre. The absolute force of human muscle (*i.e.* the weight it can *just* raise) is 8,000 grams per square centimetre; hence we see that the mammalian kidney can exert a force six times greater than the maximum performance of voluntary muscle.

Some observations of Bradford show that we have not exhausted the subject of the functions of the kidney when we have described its action as an excreting organ If in dogs one kidney be first excised, and at a later period half or two-thirds of the other kidney, it is found that the urine after the second operation is largely increased in quantity, and contains much more urea than it did under normal circumstances This urea comes from the disintegration of the nitrogenous tissues, since the animal wastes rapidly and dies in a few weeks An explanation is yet wanting for the paradoxical fact that an animal with one-fourth its normal amount of kidney substance should form and excrete double the normal amount of urea It is evident that the kidneys play an important and hitherto unlooked-for part in nitrogenous metabolism, but we are not yet in possession of sufficient facts to decide the exact extent and nature of this function

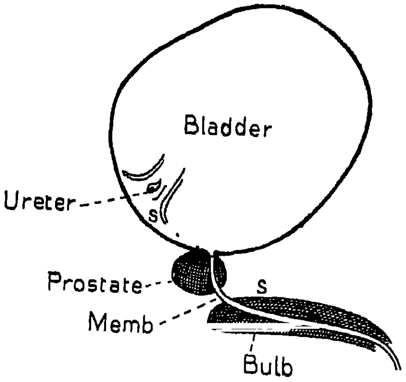
SECTION 3

MICTURITION

The urine is secreted continuously, although the amount secreted may vary from time to time according to the condition of the animal. Partly through gravity, partly through the pressure under which it is secreted, the urine is driven on through the ureters. If these be occluded, the secretion of urine continues until its pressure reaches 60 to 80 mm. Hg, when it ceases. This pressure is sufficient to distend widely the upper part of the ureters and the pelvis of the kidney. In the ureters, which are muscular tubes lined with transitional epithelium, the urine is driven on by peristaltic contractions, which travel from the upper to the lower part of the ureter. These contractions occur from three to ten times a minute, and seem to originate in the muscular substance of the ureter itself, since they are to be seen in an excised ureter. The urine in this way gradually accumulates in the bladder; its reflux into the ureters is prevented by the oblique manner in which these enter the bladder, a sort of valvular opening being thus formed. At intervals the urine that is collected in the bladder is expelled by contraction of its muscular wall. This act of micturition is in the young child purely reflex, and dependent on the tension in the bladder. With advancing age however the individual acquires more or less voluntary control over the reflex act. It will be convenient to consider first the purely reflex act of micturition.

The muscular wall of the bladder is generally described as consisting of three coats, an external longitudinal, sometimes known as the *detrusor*, and chiefly marked on the anterior and posterior surfaces, a middle coat of circular fibres, which are better developed towards the base of the bladder, and a very incomplete internal coat of longitudinal fibres. In the bladder no distinct demarcation can be made between the various coats, and a bundle of fibres, which is at first longitudinal, may dip inwards and run in a circular direction. No distinct thickening of the circular coat to form a sphincter can be made out at the vesico-urethral orifice, and on this account the circular muscle-fibres surrounding the prostate have been described as an external *sphincter vesicæ*, and have been regarded as the chief sphincter of the bladder. This however would leave the female sex entirely without a sphincter. Moreover in many animals the prostate is confined to the dorsal side of the urethra, and does not run completely round it. It has therefore been suggested that the urine is retained by the mechanical arrangements at the neck of the bladder. Thus if fluid be injected into the bladder through one of the ureters, a point is finally reached at an internal pressure of about 120 cm. of water, at which the fluid begins to escape from the urethra The same result is observed if the experiment be tried on a dead animal, but in the latter case the urethra does not contract after the passage of the fluid, and so remains patent and filled with fluid. If therefore the experiment be tried a second time, a very small pressure suffices to bring about an escape of urine from the urethra. On this account also the direction of the tension of the bladder-walls is of considerable importance in determining the amount of pressure necessary to overcome the resistance of the urethral orifice. If the abdomen be opened, considerable pressure may be applied to the bladder in a downward direction without any escape of urine, whereas if the bladder be taken in the hand and drawn up, comparatively slight pressure serves to expel its contents. When, as usually occurs, the expelling force is represented by the contracting walls of

FIG 220



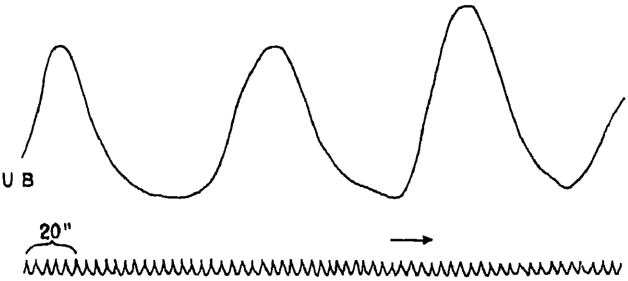
the bladder itself, the circular and longitudinal fibres both co-operate in straightening the vesico-urethral canal and forcing a fluid wedge into the beginning of the urethra.

A recent investigation by Kalischer of the structures at the neck of the bladder has brought to light the existence of two distinct structures, both of which must play some part in the normal retention of urine. The first of these is a dense ring of unstriated muscular fibres, the *sphincter trigonalis*, which encircle the beginning of the urethra in an oblique direction, as indicated by the dotted line *s s* in Fig 220, and are continuous with the muscle-fibres of the trigonum (the space between the openings of the ureters) These fibres are quite distinct from the circular fibres of the bladder

Besides this involuntary sphincter, Kalischer describes another, consisting of striated fibres which form a complete circle round the membranous portion of the urethra, and an incomplete ring round the anterior part of the prostate. This is the *sphincter urogenitalis*. Both structures, it will be observed, belong not to the bladder but to the urethra, of which the trigonum is genetically a part.

We must now inquire into the mechanism of the act of expulsion. As the urine slowly trickles into the bladder, this viscus first relaxes to accommodate the fluid, so that its contents increase without a corresponding rise of intra-vesical pressure. With increasing distension however the pressure in the bladder begins to rise, and this increased tension on the muscular walls has the ordinary excitatory effect on the muscle-fibre. Slow rhythmic contractions of the bladder make their appearance and increase in force with increasing tension on the muscular walls (Fig. 221).

FIG 221.



Tracings of rhythmic contractions of urinary bladder (Sherrington)

The exact point at which, with increasing pressure, this excitatory effect begins, depends largely on the rate at which the pressure is raised A bladder which normally would hold 250 c c of fluid, will not hold more than 100 c c if injected rapidly by means of a syringe In each case micturition would begin or, in the conscious animal, feelings of distress would occur, at the same intra-vesical pressure, although the amounts of fluid in the two cases are so very different

These rhythmic contractions, causing a waxing and waning of intra-vesical pressure, start impulses which travel up the afferent nerves of the bladder to the lumbo-sacral cord, and here a continual summation of these impulses goes on, until finally, as the bladder is contracting, the stored-up impulses break through all resistance and give rise to a reflex discharge down the efferent motor nerves of the bladder. A strong contraction of all the muscular fibres of the bladder is produced, causing a rise of pressure to 130 or even 150 cm. of water, which overcomes the resistance of the tissues at the neck of the bladder and continues until this viscus is emptied. This evacuation may be aided by an associated contraction of the abdominal muscles. Whether or not these events are accompanied by an active relaxation of the 'sphincter' or 'sphincters' is still undecided. At the end of the act the last drops are expelled from the urethra by rhythmical contractions of the perinæal muscles, especially the accelerator urinæ and levator ani, thus emptying this canal and restoring the sphincter action of the tissues at the neck of the bladder.

The nerve-supply of the bladder is shown in the accompanying diagram (Fig. 222). It will be seen that it receives nerves from two sources: firstly, from the upper lumbar nerves; and secondly, from the second and third sacral nerves. The fibres from the latter source run direct to the bladder in the nervi erigentes. Those from the upper lumbar cord have a more circuitous course, by the *rami communicantes* to the sympathetic chain, thence to the collection of ganglion cells surrounding the inferior mesenteric artery, and from this by the two hypogastric nerves to the bladder.

Stimulation of the upper set of nerves causes a feeble contraction of the bladder-wall which, if one hypogastric nerve be stimulated, is confined to the stimulated side, and is always most marked at the base of the bladder. Excitation of the pelvic nerves, on the other hand, causes a strong contraction of the bladder, which is generally sufficient to overcome the resistance of the sphincter, and so bring about micturition. In many animals the upper nerve-supply also carries some inhibitory fibres to the bladder-wall.

The sensory nerves of the bladder probably run in the upper (sympathetic) supply.

According to some authors these two sets of fibres are antagonistic in function Stimulation of the hypogastric nerves is said to cause contraction of the circular fibres of the bladder-wall, and therefore increased contraction of the sphincter vesicæ, whereas stimulation of the nervi erigentes causes relaxation of the sphincter and a strong contraction of the detrusor urinæ The sacral fibres are therefore those which are most important for the act of micturition The whole question of the behaviour of the sphincter however is in need of renewed investigation, in view of the anatomical results mentioned above

FIG 222

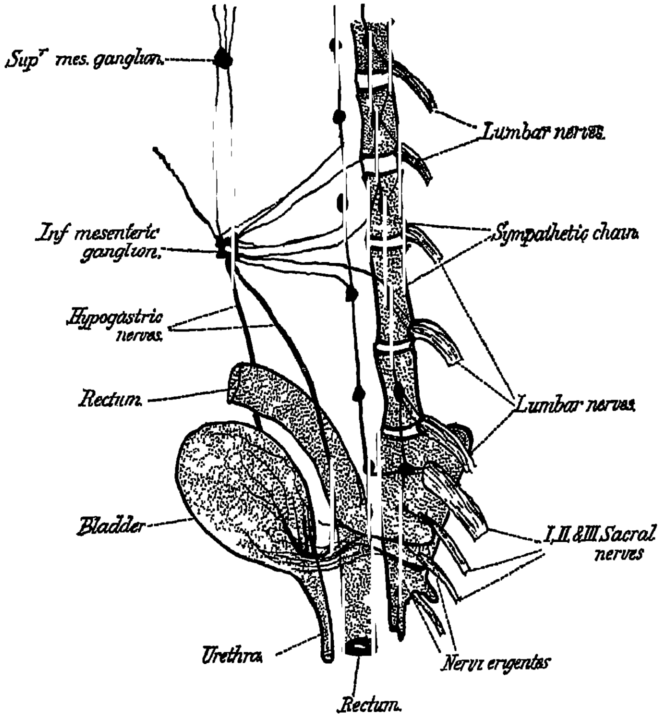


Diagram of nerve-supply to bladder (Nawrocki and Skabitchewsky)

In the adult the processes of retention and evacuation of urine are modified and controlled by voluntary effort. The normal action of the sphincter mechanism may be aided by the contraction of the perinæal muscles which keep the urethra closed. The reflex process of evacuation may be set in motion by voluntary contraction of the abdominal muscles, by which the pressure in the bladder is increased and the normal sphincter action overcome. It is probable too that the individual has a certain degree of voluntary power over the unstriated muscles of the bladder, and that the contraction of the muscular wall may be directly augmented by impulses proceeding from the cortex to the upper part of the lumbar cord.

This view is favoured by the fact that stimulation of the crus cerebri has been observed to cause contraction of the detrusor urinæ. In this experiment the abdomen was opened, so there could be no question of the contraction of abdominal muscles.

SECTION 4

THE SKIN

The skin, which covers the whole external surface of the body, consists of a layer of stratified squamous epithelium, the *epidermis*, resting on a layer of fibrous tissue, the dermis. The epidermis is composed of several layers.

(1) The *stratum Malpighii*, resting on the papillæ of the dermis, and composed of several layers of cells which, columnar below, become polygonal and flattened towards the surface.

(2) The *stratum granulosum*, one or two layers of flattened cells with many eleidin granules.

(3) The *stratum lucidum*, a layer of flattened nucleated hyaline cells.

(4) The *stratum corneum*, produced by the conversion of the cells of the subjacent layers, and consisting of horny scales.

Keratin, which forms the main part of the horny layer of the skin as well as of the skin appendages, such as nails, hairs, wool, feathers, horns, is an insoluble resistent body closely allied to the proteins. On heating with acids it gives the same decomposition products as the proteins, viz. leucine, tyrosine, and other amino-acids as well as the hexone bases. It gives the xantho-proteic and Millon's reactions, but is distinguished from other proteins by the high percentage of sulphur contained in its molecule (2.5 to 5 per cent.). The greater part of the sulphur is present in the form of cystine.

The *dermis* consists of a close meshwork of interlacing white fibres, together with connective tissue cells, blood-vessels, lymphatics, and nerves. At its under surface it passes insensibly into the subcutaneous tissue, which also consists of interlacing fibrous bundles, but with coarse meshes, giving a loose texture to the tissue. These meshes often contain a large amount of adipose tissue.

Two forms of glands are found in the skin, the sebaceous and the sweat glands. These may be considered separately.

Sebaceous glands.—These always occur in connection with the hair follicles. The hairs are formed by a transformation of certain cells of the stratum Malpighii, which have grown down into the dermis or subcutaneous tissue to form a hair follicle. The hairs are always set obliquely. At the neck of the follicle, where the stratum corneum of the surface skin comes to an end, we find the openings of the sebaceous glands. These are saccular, with a definite basement membrane which is lined by a layer of columnar cells not differing greatly from the lowermost cells of the Malpighian layer. The lumen of the gland is however also filled with cells, which are large and swollen, staining feebly with hæmatoxylin, and presenting quantities of fat granules. These degenerated cells are the secretion. Instead of the protoplasm of the cell manufacturing and storing up the secretion, as is the case with salivary glands, it is itself converted into sebum, the cells so used up and destroyed being replaced by proliferation of the cells nearest the basement membrane.

The secretion is composed of various neutral fats mixed with fatty acids, and has an acid reaction. It is interesting to note that a considerable amount of the fatty acids are in combination, not with the tribasic alcohol glycerin, but with the monatomic alcohol cholesterin These cholesterin fats, which are present also to a large extent in lanolin or wool fat, have the advantage of not decomposing readily, so serving as an efficient protection to the skin.

Running from the superficial part of the dermis to the under surface of the hair follicle is a bundle of smooth muscle-fibres, the arrector pili. Contraction of these muscles can be excited by direct application of cold (as in production of 'goose skin') or by the nervous system through the pilomotor nerves, and results in erection of the hairs. As these muscles contract, they press at the same time on the sebaceous glands and squeeze out some secretion on to the root of the hair.

The course of the pilomotor nerves has been very thoroughly worked out by Langley It may be stated as a general rule that they follow the same course as the vaso-constrictor nerves, leaving the spinal cord by the anterior roots from second dorsal to third lumbar, and passing as fine medullated fibres into the sympathetic chain by the white rami communicantes In the ganglia they end, and new relays of non-medullated fibres, starting from the ganglion cells of the sympathetic chain, go by the grey rami to the nerve-roots, in which they pass to their destination in the skin

The *sweat-glands* are composed of coiled tubes situated in the subcutaneous tissue. Their secreting portion forms about half the coil and is bounded by a basement membrane and lined by a single layer of cubical cells. Between the cells and the basement membrane is a layer of spirally arranged smooth muscle-fibres, which are especially well marked in the glands of the axilla. The duct is lined by two or three layers of cells until it arrives at the epidermis, where it is continued to the surface as a simple corkscrew channel between the epithelial cells.

Sweat, the secretion of the sweat-glands, is a clear colourless fluid, with peculiar odour and a salt taste. It is generally acid in reaction, from the admixture of the secretion of the sebaceous glands. If the skin from which it is obtained be first thoroughly cleansed, the sweat that is subsequently collected has a neutral or slightly alkaline reaction. It contains a few epithelial scales derived from the skin, and about 2 per cent. solids, of which sodium chloride makes up the greater part. Traces of fatty acids—formic, butyric, and propionic—are also present. Under pathological conditions urea, sugar, and other substances are found. Many drugs after administration reappear in the sweat.

The secretion of sweat is constantly going on. If only a small amount is formed, it is at once evaporated, and goes off into the atmosphere as insensible perspiration. If, on the other hand, the amount secreted be large, or the surrounding atmosphere moist so that evaporation cannot easily take place, the sweat collects on the surface of the body as sensible perspiration.

The quantity of perspiration given off is considerable, but varies so much that it is impossible to give an average figure for the amount. It is increased by imbibition of large quantities of fluid, especially if warm, by a warm atmosphere, or by anything which tends to increase the amount of heat formed in the body, such as muscular exercise.

The fact that sweating is so constantly associated with a warm skin seemed at first to show that the secretion of this fluid was called forth by the increased supply of blood to the surface of the body and to the sweat-glands. This view however is negatived by the fact that sweating may coincide with a pale anæmic skin, as in the cold sweats of phthisis or of the death agony, or associated with mental emotion, especially extreme fear. The activity of these glands, as of the salivary glands, is under the control of the central nervous system. Stimulation of the peripheral end of the cut sciatic nerve of the cat causes abundant secretion of sweat on the toes supplied by that nerve. If, on the other hand, the sciatic nerve on one side be cut, and the cat asphyxiated. sweating occurs in the toes of the other three limbs, but not in the limb the nerve of which has been cut. Stimulation of the sciatic nerve causes contraction of the blood-vessels, so that the secretion of sweat cannot in this case be determined by an increased blood-supply. We can indeed excite secretion of sweat by stimulating the sciatic nerve of an amputated leg.

Secretion of sweat may also be excited reflexly. Pungent substances taken into the mouth may cause abundant perspiration on the face.

The course of the sweat-nerves in the cat has been investigated by several observers, especially by Langley In this animal the hairless pads of the feet are the only parts of the body where sweat is secreted The sweat-nerves to the hind foot leave the cord chiefly by the anterior roots of the first two lumbar nerves, and passing along the white rami to the sympathetic chain make connections with cells in the sixth and seventh lumbar and first two sacral ganglia From these ganglia grey rami carry the impulses along to the corresponding spinal nerve-roots and to the sciatic nerve

The sweat-nerves to the fore-limbs leave the cord by the sixth, seventh, and eighth dorsal nerve-roots, and all have their cell-stations in the stellate ganglion, whence non-medullated fibres carry the impulses to the nerves of the brachial plexus and so to the paw The nerve-cell connections of these fibres have been determined by the nicotine method already described (p 265)

The sweat-glands may likewise be affected peripherally. Injection of pilocarpine calls forth secretion of sweat between the toes, even after the sciatics have been cut. It is found that the secretion produced by stimulation of the sciatic is much increased by warming the air surrounding the toes. The importance of this secretion for the regulation of the body-temperature will be spoken of in the next chapter.

Cutaneous respiration.—In the frog, a large amount of gaseous interchange takes place through the skin, so that the animal may live a considerable time after the extirpation of the lungs. In man, the skin and dead cuticle are much too thick to allow any great interchange to take place between the gases of the blood and the surrounding atmosphere. It is reckoned that on the average from 5 to 8 grms. of CO_2 are given off by a man from the skin in twenty-four hours, and a considerably smaller amount of oxygen is absorbed through the same agency.

It was formerly thought that various poisonous products were excreted with the sweat, and that retention of these in the body might give rise to symptoms of poisoning. It seems however that if a man's skin be clean, the sweat is perfectly innocuous, and it is found that a man may be varnished all over without suffering much harm. In rabbits, which do not sweat, varnishing the body all over causes rapid death of the animal, but this death is due simply to excessive loss of heat, and may be prevented by wrapping the animal in cotton wool. Varnishing this animal seems to cause dilatation of all the superficial capillaries, and hence a great discharge of heat from the surface of the body. The only function of any importance therefore, that can be ascribed to the secretion of sweat, is the regulation of the heat discharge from the body.

CHAPTER XI

FATE OF FOODSTUFFS IN THE ORGANISM—METABOLISM

SECTION 1

PROTEIN METABOLISM

HAVING studied the paths by which the foodstuffs are absorbed and waste products removed from the body, it remains to inquire into the changes that take place in the food after its absorption. We assume from our experience with the various tissues, especially muscle, that the combustible parts of the food are built up, together with oxygen, into the living protoplasm of the cell to form a highly unstable molecule with large potential energy. In the breaking down of this molecule there is a rearrangement of atoms to form more stable compounds, the carbon and oxygen combining into carbon dioxide with the evolution of energy, which may be displayed either as heat or work.

We are still far from being able to follow the changes that the foodstuffs undergo on entering into the living protoplasmic molecule Up to this point however we can, though with many gaps in our chain of facts, follow the fate of foodstuffs in the body, and a short account of these facts, which are grouped together under the term 'metabolism,' is the object of the present chapter.

In all experiments on metabolism we must be able to make an exact comparison of the Income and Output of the body. To this end the food must be weighed and analysed, and the oxygen taken in measured by means of some respiratory apparatus. The output of the body includes the carbon dioxide and water expired by the lungs; the urine, containing chiefly the nitrogenous excreta, the fæces, the carbon dioxide and water given out by the skin as perspiration, and a slight loss dependent on the wearing away of the cuticle. In a balance-sheet of the organism the fæces should be subtracted from the income, since they represent the undigested parts of the food.

It has been thought that in a normal animal the excreta may possibly have a twofold origin, and may come partly from the breaking down of the living protoplasm of the body, partly from the direct oxidation of the food that is continually being taken in. It must be remembered however that we have no evidence of any oxidative destructive changes in the tissue juices or blood, and that the whole weight of experiment points to the cells being the sole seat of all metabolic changes. It will be convenient to consider first the simplest condition, in which the animal takes no food, in order that we may have only the metabolism of the living tissues themselves to deal with.

In starving animals the income of the body is limited to the inspired oxygen and, in most experiments, to a certain amount of water. During an experiment of this sort, the animal is weighed every day, and the amount of nitrogen excreted and carbon dioxide given off by the lungs carefully estimated. Preliminary experiments have shown us the amount of nitrogen contained in muscle, so that from the amount of nitrogen excreted we can estimate the degree of disintegration of the muscular tissues that has gone on. From the quantity of CO_2 eliminated we can determine the loss of the carbonaceous part of the body. This may be regarded as composed entirely of fat, since the amount of glycogen and carbohydrates in the body is small in comparison with the fat present. These two amounts (proteins + fat lost) subtracted from the daily loss of weight leave a remainder which represents the output of water. Adult animals, supplied with water only, live for four or five weeks. During this time they suffer gradual loss of weight, and at death have lost about 50 per cent. of their weight. The excretion of CO_2 and water sinks continually until death takes place. The urea excretion falls considerably within the first four or five days, and then remains almost constant at a low level for about four weeks. At the end of the fourth week there may be a sudden rise in the amount of urea excreted. At this period every trace of fat has disappeared from the body.

The animal has no further store of carbonaceous material to draw upon, and so must consume the protein of its tissues in order to supply the necessary proportion of heat and work. In the emaciation consequent upon starvation it is observed that the tissues whose energies are most necessary for the carrying on of the vital functions suffer least. Thus the heart and the central nervous system lose only 3 per cent. of their weight. Of the fat, on the other hand, 97 per cent. disappears, of the muscle 30 per cent.; and a considerable decrease of weight is also observed in the bones, liver, blood, and alimentary canal.

The nitrogen that is eliminated during starvation must necessarily arise from the disintegration of the proteins of the body. As we have just seen, this amount during certain periods of starvation is fairly constant from day to day. It might be thought that, if an amount of protein were given to the animal containing a proportion of nitrogen equivalent to that which the starving animal was excreting, the loss of nitrogen to the body would be checked, the loss of nitrogen in the urine being replaced in the tissues by the nitrogen of the food. This is however not the case. After the administration of the protein to the starving animal, the quantity of urea excreted is almost doubled, showing that nearly the whole of the protein taken in is disintegrated within twenty-four hours and excreted with the urine. In order to produce a condition in which the amount of nitrogen eliminated is equal to the amount of nitrogen taken in with the proteins of the food, it is necessary to give the animal at least two and a half times the amount of protein corresponding to the nitrogen that is excreted during starvation. In this case the animal is said to be in a condition of 'nitrogenous equilibrium.'

The condition of the protein metabolism in an animal that is living on a purely protein diet and is in a state of nitrogenous equilibrium deserves a little further consideration. The fact that, to maintain the animal in this condition, two and a half times as much protein is required as is necessary to replace disintegrated nitrogenous tissues in the body, has been regarded as showing that not all the protein in the food can be devoted to this object It has been supposed by Voit that the protein taken in with the food has a twofold destination in the body, part of it going to supply the tissue waste, and being built up into the living protoplasm of the tissues (morphotic or tissue protein); while the other and probably greater moiety passes into the juices that bathe the protoplasmic elements of the cells, and is rapidly broken up and oxidised there without at any time forming an integral part of the protoplasm. This is spoken of as circulating protein.

I have however already drawn attention to the numerous experiments on the subject, carried out chiefly by Pfluger and his pupils, all of which tend to prove that the sole seat of oxidative processes in the body is the living cell.

Some experiments, which were carried out by Schöndorff under Pflüger's guidance, are of especial interest in this question According to Voit the greater excretion of urea in a protein-fed animal is due to the fact that there is an increased circulation of a fluid that is rich in proteins round the cells According to Pflüger's views however, the presence of a greater or less amount of protein in the nourishing medium would not be the determining factor for the amount of urea formed, which would be regulated simply and solely by the condition of the cells themselves To decide this point, defibrinated dog's blood was led alternately through the hind limbs and the liver of another dog, in order to get the products of metabolism of the limb tissues and then convert them into urea by passing the blood through the liver

1 In one set of experiments the blood from a dog that had been starved for five days was led through the organs of a well-fed dog In these experiments Schöndorff found that, without exception, the urea in the blood was largely increased at the end of the experiment

2 In a second series of experiments the blood of a fasting animal was led through the hind limbs and liver of a fasting animal. In these the amount of urea in the blood was unaltered

3 In a third set blood of a well-fed animal was led through organs and liver of a fasting animal In these cases the amount of urea was always diminished

It was concluded from these experiments that the extent of protein metabolism depends on the nutritive condition of the cell and not on the condition of the protein contained in the circulating tissue juices

We must therefore conclude that the whole of the protein metabolism takes place in the living cells, and not in the lymph or blood-stream. How far it is necessary for all the protein to be built up into tissue protein it is however difficult to say We may at any rate adopt Voit's view as to the twofold destination of protein, provided that we introduce certain modifications into his description of the events that take place.

Protein, as indeed all food, has a twofold object. In the first place the whole of the activities of the body are associated with the discharge of energy. The source of this energy is the food, and, so far as we can tell, the value of a given foodstuff for this purpose is determined, apart from its digestibility, solely by its heat value, *i.e.* the amount of energy it will set free in combining with oxygen to form the end products of its metabolism in the body.

The heat-values, *i.e.* the amount of heat evolved by the combustion of one gram of the substance, for the three main classes of foodstuffs are as follows—

Fats	9·3 calories
Proteins	5·5 ,,
Carbohydrates . . .	4·0 ,,

In the body, while the combustion of fats and carbohydrates is complete, part of the protein molecule is oxidised only as far as urea, which has a heat-equivalent of 2·5 calories. Since one gram of protein gives rise to 0·3 gram of urea, it is necessary, in order to get the real heat-value of protein in the body, to subtract 0·8 from the above figures, giving a corrected value for proteins of 4·7 calories. In man and herbivora the total needs of the body cannot be satisfied on a purely protein diet. In the normal diet given on page 508, the protein represents only about one-sixth of the total energy of the food.

The calorie here employed is the amount of heat which is necessary to raise the temperature of one kilogram of water one degree Centigrade.

As a source of energy it is apparently a matter of indifference whether the organism is supplied with proteins, fats, or carbohydrates.

Far otherwise is it with the other destination of protein. The greater part of the living structure of the body is composed of proteins, or of more complex nitrogenous bodies in the building up of which the proteins play a preponderating part. In the young and growing animal these tissues are constantly being added, and the raw material for growth can be supplied by protein, and by protein only. Moreover, in the period of adult life, when the body is neither gaining nor losing weight, every vital act is associated with a certain degree of what we may term 'wear and tear' of the living structure. Few of the cells of the body have a life coterminous with that of the whole organism. Most of the cells are continually dying and being replaced by fresh ones. For this *nutri-*

tional metabolism a supply of proteins in the food is an absolute necessity. Every diet therefore must contain a certain minimum amount of protein to supply the nutritional needs of the organism, while the energy requirements can be supplied at the expense of either proteins, fats, or carbohydrates.

The physiological value, however, of these three classes is not entirely expressed by their heat values. The organism has the power of storing up any excess of fat or carbohydrate above its energy requirements in the form of fat, which can be utilised for the future activities of the organism. Its power of storing up protein is however extremely limited. In some animals overfeeding with protein may produce a growth of muscles, which may be regarded as forming, in some sense, a protein storehouse. In most animals, including man, this power is practically absent. Load the animal as we will with protein, two days of starvation will suffice to exhaust any store of protein or nitrogenous materials, and the excretion of urea sinks to the starvation minimum, its amount being determined by the size and activities of the animal and the amount of fat available for the supply of the energy requirements of the body. On the other hand, feeding the animal with excess of protein only leads to increased excretion of urea. If for instance a man were taking 10 grams of nitrogen in the form of protein in the day with a sufficiency of fats and carbohydrates to maintain his weight constant, he would probably excrete also 10 grams (9 grams in the urine, 1 gram in the fæces), and would therefore be in a state of nitrogenous equilibrium. On doubling the protein intake, the nitrogenous excretion would rise in proportion, *i.e.* to 20 grams, and the man would remain in a state of nitrogenous equilibrium however much his protein intake were increased. The increased protein diet would, however, raise his energy income above his daily requirements. A certain amount of the fat and carbohydrate would therefore escape oxidation and would be stored up in the form of fat, and the man would therefore increase in weight. It is impossible in man to push this experiment very far, since a large excess of protein diet gives rise to digestive disturbances, and the experiment has to be discontinued.

It is evident that, given a sufficiency of fatty and carbohydrate food, the minimum protein possible in any diet represents the nutritional needs of the body for nitrogen. Many experiments have been made to determine this minimum. It probably varies considerably in different individuals. Just as some machines undergo greater wear and tear, and others require a greater consumption of coal to perform a certain amount of work, so it is with animals and men, and it would be dangerous to lay down rigid laws for diet from observations on a few individuals. The minimum amount of protein required in any diet may probably be put at about 60 grams, though some individuals may keep in good health on a still smaller amount. Any protein above this amount may be regarded as concerned, together with fats and carbohydrates, in supplying the energy requirements of the body.

The minimum need for protein cannot be determined from experiments on fasting animals. In these there is often a deficiency of fat, and, after a few days, of carbohydrate, and the protein metabolism may therefore be concerned, not merely in maintaining the nutrition of the working tissues, but also in supplying a certain amount of the energy required for the different activities of the body.

SECTION 2

FORMATION OF FAT

If, while the animal is in a state of nitrogenous equilibrium, larger amounts of fat or carbohydrates be given than are necessary for its daily consumption, the animal increases in weight, and the excess of carbonaceous material is deposited in its body in the form of fat. On a purely protein diet no very large amount of fat, if any, is ever deposited in the body. A formation of fat from protein, though not proved under normal circumstances, has been thought to occur under pathological conditions in the higher animals and in many lower organisms. Thus if dogs, that have been starved till all fat has disappeared from the body, be poisoned with phosphorus, a large increase in the nitrogen excretion is observed, and when the animal dies all its organs are found to be in a state of fatty degeneration, and to contain two or three times the normal amount of fat. In this case there is apparently a splitting up of the protein molecules of the tissues into a nitrogenous moiety, which is excreted, and a carbonaceous moiety, which is retained in the cells in the form of fat. It is more probable, however, that the fat deposited in the cells is the product of conversion of carbohydrate or fat molecules transported from other cells of the body. Evidence in favour of the fat in fatty degeneration of the liver being deposited rather than formed *in situ* is afforded by the fact that, if the poisoned animals be fed with abnormal fats, these fats are found forming part of the fat in the degenerated tissue. In the ripening of cheese, which is accomplished by the agency of low organisms, there is a conversion of protein into fat. If the eggs of fly-maggots be allowed to develop on a blood-clot, the maggots, when full-grown, will be found to contain ten times as much fat as there was previously in the blood-clot and eggs together; so that in this case the maggots have been able to convert the protein of the blood-clot into fat. We must conclude therefore that proteins may be converted into fat in the living organism, although it is very doubtful whether any such conversion takes place in the higher animals under normal conditions.

It was long doubted whether the fat in the food could be directly deposited in the body as such. It was supposed that the fat in the food exerted merely a sparing effect on the fat in the body formed from the proteins—that the fats absorbed from the alimentary canal served to supply the organism with an oxidisable material, and so shielded from oxidation the fat in the tissues that had been formed from protein. We have however conclusive evidence that the fats taken in with the food can be deposited in the body as such. Thus two dogs were fed, one with linseed oil, the other with mutton suet, for a considerable period. The fat in the tissues of the former was liquid at 0° C., while the fat of the latter had a melting-point at above 50°. In another experiment, in which a dog had been fed with colza oil, erucic acid, which is an ingredient of colza oil, but absent from animal fat, was found in the fat of the dog after death.

Not only are neutral fats thus absorbed from the intestine and deposited in the body, but also fatty acids. If these be administered to an animal the greater part is absorbed, and it is found that in the chyle of the thoracic duct nearly the whole of the fat is present as a neutral fat and not as a fatty acid, showing that, in the passage of the fat from the intestine through the wall of the villi into the lacteals, there has been a synthesis of fatty acid with glycerin. This is an interesting fact, since glycerin is at no time found free in the animal body, although we see that the epithelial cells of the intestine can supply sufficient of it to unite with nearly the whole of the fatty acid absorbed.

Long experience has shown the farmer the value of carbohydrates as fattening food. As in the case of fats, the question has arisen whether the carbohydrates are converted into fat, or whether they have only a sparing influence on the hypothetical fat formed from the proteins of the food. That the former is the case is shown by the following experiment. Two young pigs, ten weeks old, of the same litter, with approximately equal weights, were taken. One was killed, and the fat and total nitrogen in the body estimated. From the amount of nitrogen the maximum possible quantity of proteins present was calculated. The second was fed on barley for four months. The barley was measured and analysed, as well as the amount of undigested fat and protein that passed through the animal. At the end of the four months the second animal was killed and analysed. It was found that the animal contained 1·56 kilos more protein, and 8 6 kilos more fat. It had taken up with the food 7·49 kilos more protein, and 0·66 kilo fat. If we subtract the protein added to the body (1·56) from that taken up with the food (7·49), there is a remainder of 5·93 kilos which might possibly have given rise to fat. But 7·9 kilos of fat had been added in the body—a far larger amount than could possibly have arisen from the maximum amount of protein left over for the purpose. At least 5 kilos of fat in this experiment must have been derived from the direct conversion of the carbohydrates of the food. We must conclude that fat can be formed directly from carbohydrates, although how and where this conversion takes place is at present quite unknown. We have however parallel instances in the formation of butyric and other acids of the fatty acid series from sugar by means of certain organised ferments.

As we should expect, peptones may be used entirely to replace the proteins of the food, and the animal will maintain or even increase its weight on such a diet.

Gelatin cannot take the place of proteins in the food. As we have seen, it differs from ordinary proteins in certain important chemical relationships. If given in the food, it has, like carbohydrate and fat, a sparing effect on the protein, so that nitrogenous equilibrium is attained with a smaller amount of protein than would be the case if no gelatin were given. If a dog be fed on gelatin and fat, the excess of the nitrogen excreted over the nitrogen taken in is less than when the same dog is fed on fat alone, showing that the gelatin has sheltered from disintegration some protein constituents of the body. It has been said that gelatin can take the place of circulating, not of tissue protein. It would probably be more correct to say that, containing as it does only certain of the ordinary constituents of the protein molecule (tryptophane and tyrosine, for example, being absent), it can only partially replace protein in supplying the nutritional needs of the tissues.

Since fat represents a store of food in the body, it is evident that a reduction of the fat can be effected only in two ways, either by increasing the energy demands of the body, as by muscular work, or by diminishing the energy supply by lessening the food supply, *i.e.* by starvation. A man of 70 kilos doing a moderate amount of work needs about 40 caolries per kilo body-weight each day, *i.e.* his diet must have a heat-value of about 3,000 calories. If this supply be reduced, he will begin to use up the supply of energy represented by the fat of his body; and all the obesity cures take advantage of this fact. In some all the foodstuffs are diminished at the same time; in others, as in the Banting cure, the man is allowed to eat as much lean meat as possible, only fats and carbohydrates being restricted. In this case a very rapid diminution of body-fat results. This diminution has been ascribed to a specific stimulating effect of protein on metabolism. Such an explanation is unnecessary. A man who is eating even five pounds of lean meat a day is being starved. Whereas his daily requirements are 3,000 calories, he is getting with his food only 2,300 calories, and as a matter of fact no man can continue to eat such large quantities of meat. Three pounds of meat a day, a more usual quantity, would have a heat-value of about 1,400 calories, and it is not surprising that the organism makes good the large deficit by feeding on the stored-up fat of the body.

SECTION 3

HISTORY OF CARBOHYDRATES IN THE BODY

Normally, the blood of man and dogs contains from 0·05 per cent. to 0·15 per cent. of sugar (dextrose). If this amount be artificially increased by the injection of sugar into the blood, it is found that, as soon as the amount of sugar rises above 0·2 per cent., the excess is eliminated by the kidneys and appears in the urine. After a meal rich in carbohydrates, such as the Irishman's mess of potatoes, a very large amount of sugar passes into the blood of the portal vein. Several hundred grams however of carbohydrates may be ingested without any sugar appearing in the urine. Again, in the interval between meals when no sugar is passing into the blood, the amount of sugar remains constant, although we have reason to believe that it is incessantly being used up by the muscles and other tissues of the body. There must be some means therefore by which the overloading of the blood with sugar is guarded against, at the same time that the sugar percentage of the blood is maintained constant during periods of temporary starvation. This function is subserved by the liver, the great chemical factory of the body. This is shown by the fact that, if a solution of dextrose be slowly injected into a mesenteric vein, no sugar appears in the urine, whereas glycosuria is at once produced if the injection be made into the jugular vein.

Just as plants have the power of transforming sugar into starch, which is deposited as a reserve material in their tubers and similar organs, so the liver has the power of seizing upon the excess of sugar passing through its capillaries and transforming it into a colloidal substance, which is deposited in the meshes of the cell-protoplasm. This colloidal substance belongs to the group of starches, and is called glycogen or animal starch.

Preparation of glycogen.—A rabbit is well fed with carrots or arrowroot for a couple of days. It is then killed by decapitation, the liver cut out and thrown into boiling water, and boiled for about ten minutes. The pieces are then ground up with sand to a fine paste, returned to the same water, and boiled for half an hour. While the mixture is still boiling, a few drops of acetic acid are added until the reaction is very faintly acid. In this way practically all the proteins are coagulated. The mixture is then thrown on a filter, and an opalescent fluid runs through containing only the merest traces of protein. From this fluid the glycogen is precipitated as a white amorphous powder by addition of two volumes of 90 per cent. alcohol. It may be purified by solution in water and reprecipitation by alcohol; it is finally washed with alcohol and ether and dried. It may be freed from adherent traces of protein by boiling with alcoholic solution of potash, in which the glycogen is insoluble.

The glycogen so obtained is a white powder, free from taste or smell, dissolving in hot or cold water to form a strongly opalescent solution. With iodine its solutions give a port-wine coloration. It may be distinguished from erythrodextrin by the fact that it is precipitated on saturation with ammonium sulphate, or by 60 per cent. alcohol, whereas dextrin needs nearly 90 per cent. alcohol for its precipitation. Its relationship to starch is shown by its composition $n(C_6H_{10}O_5)$ and by the fact that on hydrolysis it yields dextrins, maltose, and finally dextrose.

In the liver treated in the manner described above we find only the merest traces of sugar. If however the liver be left for some hours after the death of the animal before extraction with boiling water, the extract will be found to contain much less glycogen, but very large quantities of sugar. We see that after death a process takes place in the liver by which the glycogen is converted into sugar. This sugar is dextrose. The conversion may take place even after the cells have been subjected to the action of absolute alcohol for a considerable time. This fact shows that the conversion is due to the presence in the liver of some substance which may act as an amylolytic ferment, converting starch or glycogen into sugar. This ferment is destroyed by heat, and it is on this account that the liver is thrown into boiling water in order to obtain the maximum yield of glycogen.

Circumstances influencing the formation of glycogen.—The amount of glycogen present in the liver at any given time is intimately dependent on the food taken. If an animal be starved, the glycogen in the liver diminishes quickly at first, and more slowly afterwards. After prolonged starvation the liver contains only the merest traces. If a rabbit, deprived of glycogen by starvation, be given a meal of carbohydrates and killed a few hours later, the liver will be found to contain large quantities of glycogen.

Although carbohydrates furnish the chief material for the manufacture of glycogen, yet we have evidence that the organism is able to form glycogen out of proteins. If a dog, deprived of glycogen by long starvation and work, be fed for a few days on a diet of washed fibrin perfectly free from carbohydrates, the liver will be found to contain a fair quantity of glycogen, though the amount is many times less than that formed on a diet of carbohydrates.

Fats have no influence on the formation of glycogen. The glycogen disappears as rapidly in an animal fed on fat alone as in starvation.

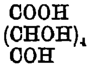
Much more efficacious than starvation in causing disappearance of the hepatic glycogen is muscular work. If a dog be starved for a day and be then made to drag a heavy milk-cart about all the next day, there will be found only the merest traces of glycogen in its liver.

Glycogen also occurs in the muscles, where it probably serves as a local supply of reserve material for the furnishing of muscular energy. The glycogen must be conveyed from the liver to the muscles and other organs of the body in the form of sugar, since we cannot detect any glycogen in the blood. The importance of glycogen as a reserve material is shown by the fact that it is present in very large quantities in embryonic muscle, at a period when the formation of new muscular fibres is going on most intensely.

We may also look upon glycogen as a source of heat. If the temperature of a rabbit be lowered by immersing it in a cold bath, the glycogen is found to have disappeared from the liver after a few hours.

Glycosuria

Under certain circumstances the power of the liver to store up the glycogen may be temporarily destroyed. If a puncture (*piqûre*, or diabetic puncture) be made in the floor of the fourth ventricle between the nuclei of the auditory and vagus nerves, the animal for the next twenty-four or thirty-six hours will suffer from glycosuria; that is to say, sugar will pass into the urine. At the end of this time the liver will be found to be quite free from glycogen. If, on the other hand, the animal be first deprived of glycogen by starvation and work, the diabetic puncture will be without effect, showing that the glycosuria is due to the rapid conversion of the hepatic store of glycogen into sugar. This is turned out into the blood-stream, where it raises the percentage amount of sugar so high that the excess is excreted by the kidney-cells and appears in the urine. Temporary glycosuria may be brought about by various other means, such as poisoning by strychnine or curare. After administration of chloral and some other drugs, a reducing body appears in the urine, which was formerly thought to be dextrose. It has been proved however that in this latter case the reducing body is not dextrose, but an oxidation-product of dextrose, *glycuronic acid* ($C_6H_{10}O_7$).

It is interesting to note that, in the formation of glycuronic acid, the oxidation has attacked the end of the molecule furthest away from the aldehyde COH group, perhaps pointing to the fact that the sugar molecule is attached to the protoplasmic molecule by this, its most unstable group. The formula of glycuronic acid is  $\begin{array}{l}COOH\\(CHOH)_4\\COH\end{array}$. It is apparently being constantly formed in the body in the oxidation of dextrose, although special means are necessary to fix it in this stage before it has undergone further decomposition. Thus phenol when administered to a dog is normally excreted in ethereal combination with sulphuric acid. If however the dog be fed on a farinaceous diet poor in proteins the administration of phenol is followed by its excretion in combination with *glycuronic acid*, *i.e.* an acid derived from carbohydrate metabolism instead of one derived from the metabolism of proteins.

The results of the administration of phloridzin throw some light on the carbohydrate metabolism of the body. Phloridzin is a glucoside found in the root cortex of apple and cherry trees. If a certain amount of this be administered to a dog, sugar appears in the urine after a few hours, and the glycosuria lasts for two or three days. If the dog be killed at the end of this time, the liver and muscles are found totally free from glycogen. We might thus come to the conclusion that the sugar was derived from the glycogen stored up in the body, and from that alone, as is the case after the diabetic puncture. But if, when the glycosuria has ceased and the body is quite free from stored-up glycogen, a second dose of phloridzin be given, a still larger amount of sugar is excreted. As the dogs were starved during the experiment, this sugar must have been derived from protein. Thus we see that sugar as well as glycogen may be manufactured in the body directly from protein.

Although both after administration of phloridzin as well as after diabetic puncture, there is disappearance of glycogen from the liver, the causation of the glycosuria in the two cases is quite different.

The blood normally contains about 0·05 to 0·15 per cent. of dextrose. This does not escape into the urine, since normal urine contains only minimal traces of dextrose. If however the percentage of sugar in the blood rise above 0·2 per cent., the excess is at once excreted by the kidneys. Thus a flushing of blood with sugar (either by excessive absorption from the alimentary canal, by artificial injection of dextrose or abnormal conversion of the liver glycogen) will bring about glycosuria.

After the injection of phloridzin however, the amount of sugar in the blood is found to be rather diminished than increased, and this diminution is most marked in the blood of the renal vein. If phloridzin be injected into one renal artery, the corresponding kidney at once begins to secrete sugar, and the kidney of the opposite side follows suit only after some minutes' interval. We must conclude therefore that the primary action of this drug is on the kidney, exciting it to secrete the sugar normally present in the blood, and thus reducing the percentage of sugar below normal. The matter however will not rest here. The function of the liver is to keep the amount of sugar in the blood normal. As soon therefore as it receives the blood which has been impoverished in sugar by the abnormal action of the kidneys, it will take of its store of glycogen, turning out sugar into the blood until the normal composition of this fluid is restored. And so these contending processes will go on, the liver pouring sugar into the blood, and the kidneys at once excreting it out of the body. This struggle will continue until the hepatic store of glycogen is exhausted, and then, if the kidneys are still under the influence of phloridzin, the liver will attack the proteins in order to keep up the sugar supply, and there will be a rise of urea excretion in the urine which will run exactly parallel to the amount of sugar in this fluid. It has been suggested that the phloretin, the nitrogenous constituent of phloridzin, may act as a carrier of sugar across the renal epithelium, combining on one side with the blood-sugar to form the glucoside phloridzin, which is then broken down again by the cells into sugar, which is excreted on the other side, and phloretin, which is free to repeat the carrying process.

In the disease known as diabetes, in which the patient passes large quantities of sugar with the urine, the immediate cause of the glycosuria is an increased amount of sugar in the blood, amounting in some instances to as much as 0·4 to 0·6 per cent. Some of these cases may be due to defective power of the liver to store up glycogen, so that the excess of sugar taken in with the food passes at once into the general circulation, and is excreted by the kidneys. Such cases may be successfully treated by limiting the amount of carbohydrates taken in with the food. This however cannot be the explanation of the ordinary cases of severe diabetes. In these the patient passes sugar even during starvation or on a pure protein diet. just as in the case of a dog poisoned with phloridzin. In these cases glycogen may be found in the liver after death, so that this function of the liver is certainly not wanting. The passage of sugar into the urine probably depends on the inability of the organism to utilise the sugar taken in with the food or split off from the proteins of the body. It is found therefore that the excretion of urea is also increased. In fact, the man is in the condition of an animal fed on proteins alone Since the carbohydrates cannot be utilised, the organism has recourse to the proteins to cover the whole expenditure of energy, and hence the increased excretion of urea.

Why the power of utilisation of the sugar is defective we do not know. It may be that the sugar has to be further elaborated in certain organs before it can be used up by the general tissues of the body. Such a function of elaboration may possibly belong to the pancreas, since this organ has been found diseased in about one-fifth of the fatal cases of diabetes. Whether or not the pancreas is at fault in all cases of diabetes is not yet known. There is no doubt however that this organ is in some way connected with the sugar metabolism of the body. If the pancreas be extirpated in a dog, the animal acquires severe diabetes, which proves fatal in a few weeks. The glycosuria continues even on a pure protein diet or during starvation, and under these circumstances a constant relation is found between the urea and the dextrose, showing that the latter has been derived from the disintegration of protein. The same conclusion may be drawn from the severe wasting of the muscular tissues which occurs. In a little time other abnormal products of metabolism appear in the urine—oxybutyric and aceto-acetic acids, as well as aceton derived from a decomposition of the latter acid. In this respect the pancreatic diabetes resembles the severe diabetes of man. The abnormal formation of these acids leads in time to an acid intoxication, the animal dying in a state of coma, the so-called 'diabetic coma.'

The exact causation of this form of diabetes is unknown, although many theories have been proposed, all equally unsatisfactory. It is necessary to extirpate the whole organ, since partial excision, ligature of the duct, or division of all the nerves to the gland does not produce diabetes. On this account it has been suggested that the epithelial cell-nests (islets of Langerhans) of the pancreas are the important structures, whose excision involves the production of diabetes. Pathologists who have attempted to test this hypothesis by an adequate examination of the pancreas in fatal cases of diabetes have arrived at divergent results. We have already seen however (p. 329) that these islets in all probability represent phases in the activity of the secreting tissue of the gland, and do not need therefore to be endowed with a special function apart from that of the rest of the gland. Moreover we do not get any nearer to a solution of the question by saying that the pancreas has an internal secretion, since we have no conception how such a secretion may work. It has been stated that in pancreatic diabetes the sugar in the urine disappears after excision of the liver, showing that in this, as in the other forms of glycosuria, the liver is the great sugar factory of the body.

The whole question of diabetes is however too difficult to be dealt with at greater length here. Although the researches into its causation have thrown some light on the normal carbohydrate metabolism of the body, the light is at present only sufficient to intensify the black shadows of ignorance that obscure almost every part of our knowledge of the subject.

SECTION 4

THE SOURCE OF MUSCULAR ENERGY

It was always maintained by Liebig that the foodstuffs might be divided into two main groups—the carbohydrates and fats that gave rise to the heat produced in the body, and the proteins which were the source of muscular energy. This view was however refuted once and for all by the classical experiment of Fick and Wislicenus (1865). These observers ascended to the summit of the Faulhorn, which is 1,956 motres high. The urine they secreted during the six hours' ascent and during the succeeding six hours was collected, and from the amount of nitrogen contained in this was calculated the amount of protein that was used up during this time. It was found that in the case of Wislicenus 37 grms. protein had undergone oxidation. It was calculated that the oxidation of this quantity would produce 250 heat units (the unit of heat here employed is that amount of heat necessary to raise the temperature of one kilogramme of water one degree Centigrade). This heat is equivalent to about 100,000 kilogrammetres of work. But Wislicenus weighed 76 kilos, so that in raising his body to the height of 1,956 metres he had performed 76 × 1,956 = 148,656 kilogrammetres of work. There was moreover a large expenditure of energy in the movements of the heart and respiratory muscles, which is not taken into account here; so that the amount of work done was far larger than could be accounted for by the oxidation of proteins.

If the income and output of a man be compared for several days, on some of which work is done, while on others no work is done, it is found that the consumption of oxygen and the production of CO_2 are much larger on the working days than on the resting days, and that in fact the increased oxidation of carbon which takes place is sufficient to account for the energy expended. The nitrogen excretion on the other hand is only slightly increased. This slight increase may be due to the increased wear and tear of the protoplasmic mechanism of the muscle, and is not nearly sufficient to account for the energy expended.

If a dog be starved for six successive days, and on the last three be made to do hard work, it is found that the increase in the excretion of urea on the last two days is still quite small. As we have already seen, one day's starvation and hard work are sufficient to get rid of all glycogen from the body. Hence it is evident that in the last two days the greater part of the energy for the performance of muscular work must have been derived from fats. We must conclude that normally the fats and carbohydrates are the chief sources of muscular energy.[1]

If however an animal be fed on a pure protein diet, work increases the excretion of urea, since the energy in this case has to be derived from the disintegration and oxidation of proteins. Muscle draws its energy from all three classes of foodstuffs. So long as carbonaceous food is supplied in sufficient quantity, or is present in the body in the form of fat or glycogen, the muscle chiefly makes use of this for the energy required in the contraction. If this is not given, or if the carbonaceous stores of fat and glycogen are used up, muscular work must be maintained by the disintegration and oxidation of protein.

In 'training' for severe muscular exertions it has long been customary to give an excess of protein diet. Since in most cases the process of training involves the growth of muscular tissue, and therefore an addition to the protein structures of the body, a certain excess is justifiable. But there seems to be no object in increasing the protein beyond what is necessary to supply the material for this hypertrophy. A well-trained man certainly works more economically (*i.e.* with less wasteful heat formation) than an untrained man, as is shown by the respiratory exchanges of the two individuals. But for the production of this trained condition of 'fitness' it is the constant exercise and the healthy life, together with the absence of superfluous fat round the muscle fibres, that are the chief factors, and there is no sufficient proof that a muscle works more economically at the expense of protein than at the expense of carbohydrate or fat. In fact the ultimate and chief source of energy in protein, as in carbohydrates and fats, is the oxidation of the carbon of the molecules, and there seems to be no advantage to the body in complicating this process with the splitting off of nitrogen, or in loading the tissues and circulating fluids with the numerous intermediate products which occur in the oxidation breakdown of the protein molecule.

---

[1] But not on a mixed diet, the sole source The absence of influence of moderate exercise on the respiratory quotient shows that in work an animal utilises the same foodstuffs as at rest, i e that the muscle draws its energy from all three classes of food This increased katabolism would be followed by a greater appetite and therefore increased intake of all three classes Only when the income of protein is restricted do we find a sparing of the precious protein, so that the energy of the contracting muscles appears to come from the combustion of carbonaceous material alone

SECTION 5

ANIMAL HEAT

All the energy that is set free by the decomposition and oxidation of the foodstuffs appears as work or heat. It has been reckoned that about nine-tenths of the energy set free in the body appears in the form of heat, and one-tenth is represented by the work done. In the chapter on Muscle we saw that its efficiency as a heat-engine varied within very wide limits, the proportion of heat evolved to work done in muscular contraction being from 5 : 1 to 25 : 1. Even if we take the lowest of these estimates, we see that a very large proportion of the heat produced in the body must be evolved by the muscles. The increased production of heat attendant on bodily exercise is familar to every one. If the spinal cord of an animal be excited by faradic currents, so as to cause tetanic contraction of all the limbs, the production of heat in the muscles is so large that the temperature of the animal may rise to 110° or 112° Fahr.—a rise which is fatal.

Next to the muscles in importance as a source of heat to the body is the liver. In fact, under normal circumstances the temperature of the blood in the hepatic vein is higher than in any other part of the body. Wherever active processes of katabolism are going on there is an evolution of heat. Probably there is a similar evolution of heat accompanying the activity of every gland in the body.

We must also look upon the brain as a source of heat, since thermometers inserted in it may register a higher temperature than that of the blood which is supplied to the brain. The amount of heat produced here is however insignificant compared with that formed in the muscles and liver.

On the processes of metabolism—the decomposition and oxidation of foodstuffs—depend the maintenance of life. Hence all living animals are continually producing heat and imparting it to the surrounding bodies ; and unless this heat production is more than counterbalanced by loss of heat in surface evaporation, they must have a higher temperature than the surrounding medium, although the difference may not amount to more than two or three degrees in cases where metabolic processes are going on sluggishly.

With respect to their internal temperature, animals may be ranged into two main classes: (1) those which have a fixed temperature, which is within certain limits independent of the surrounding medium—*homœothermic* animals; (2) those in which the temperature varies with that of the surrounding medium—*poikilothermic* animals. To the first class belong birds and mammals, including man; they are often spoken of as warm-blooded animals. The lower Vertebrata, including reptiles, amphibians, and fishes, and the Invertebrata, belong to the second class of poikilothermic animals.

We must now inquire into the means by which this regulation of the internal temperature in warm-blooded animals is effected. The temperature of an animal is the algebraic sum of two factors—the amount of heat produced and the amount of heat lost in a given time. If, while the heat production remains constant, the amount of heat imparted to the surrounding medium be increased, the temperature will fall. If, on the other hand, heat loss remaining constant, heat production be raised, the temperature will rise in the same proportion. So the temperature may be regulated by alterations in the heat production or in the heat loss; and if the temperature is to remain constant, there must be an accurate correlation between the two processes.

Regulation of Heat Production

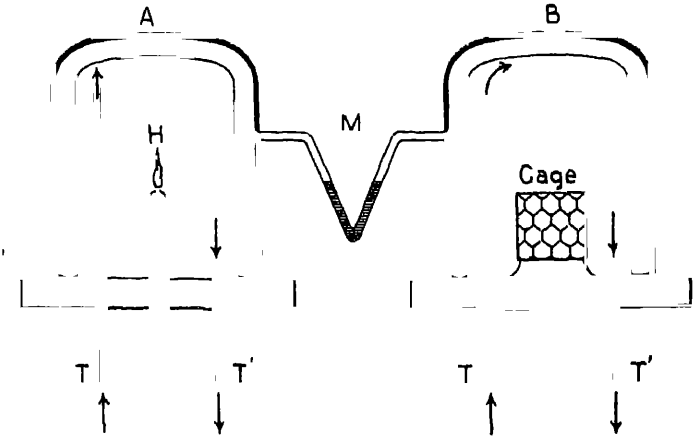
The heat production in an animal may be measured in two ways, either directly or indirectly.

The direct measurement of the heat production in an animal is fraught with many difficulties, and it is doubtful if any satisfactory form of calorimeter has yet been devised for the purpose. In order to determine the heat of combustion of any substance, the ordinary ice or water calorimeter is perfectly satisfactory. In the case of a mammal however we have to maintain a constant circulation of air through the apparatus and otherwise to keep the animal under as normal conditions as possible. One of the best calorimeters for this purpose is that devised by Haldane and

Hale White, in which the heat production of an animal is balanced against the heat produced by burning hydrogen. The number of units of heat given off by the animal to the apparatus can be directly calculated from the number of grammes of water produced by the burning hydrogen in the same time.

The calorimeter consists essentially of two precisely similar chambers, A and B, each of which has double walls of sheet copper with an intervening air-space Both air-spaces communicate with the two limbs of the manometer M, which therefore serves as a differential thermometer, the slightest difference of temperature in one chamber causing an expansion of the air and consequent displacement of the fluid in the tube Air is led through the chambers by the tubes T, leaving by the tubes T′, care being taken that the ventilation in both chambers is the same. The air is dried before entering by passing over pumice and sulphuric acid The air which leaves also passes over sulphuric acid The animal is placed in the cage in B and the hydrogen flame in A lighted, and the height of the flame is adjusted by altering the current of hydrogen until the fluid in the manometer M remains absolutely stationary. The heat production in the two chambers must now be the same, and can be determined by weighing the sulphuric acid bottle on the exit tube of A before and after the experiment, the amount of water formed giving the quantity of hydrogen burnt and therefore the total heat produced

FIG 223



Differential calorimeter of Haldane, Hale White, and Washbourn

The practical carrying out of these experiments involves so many difficulties, that in most cases it is more convenient to have recourse to the indirect method, *i.e.* to measure the output of the animal in CO_2 and the income of oxygen, and, judging from the respiratory quotient the character of the foodstuffs destroyed, determine from the known heat of combustion of these foodstuffs the total heat production of the animal during the experiment. The data will of course be more accurate if the urea excretion be also measured and taken as an index to the protein used up.

It has already been mentioned that, if a frog or other cold-blooded animal be exposed to a higher temperature, its internal temperature will also rise. If, at the same time, we measure the respiratory interchanges of the frog, we find that at the higher temperature more carbon dioxide is evolved and more oxygen taken up, showing that in this case a rise of temperature in the surrounding medium causes a rise in the temperature of the frog, and at the same time increases the activity of its metabolic changes. Cooling has the reverse effect. If a frog be cooled to 0° C., the chemical changes in its tissues are so reduced that it may be kept alive for some days in an atmosphere devoid of oxygen. The case is quite otherwise with warm-blooded animals. Exposure of one of them to a cold medium raises the amount of carbon dioxide given off and oxygen taken in, while the temperature of the animal remains unaltered. This power of the animal to *react* to changes in the temperature of the surrounding medium is dependent on the integrity of the nervous system and its connection with the muscles. If a dog or rabbit be poisoned with curare (which paralyses the muscle end-plates), or if its spinal cord be divided just below the medulla, its temperature sinks continuously. It is then found that the animal reacts to changes in the temperature of the surrounding medium precisely like a cold-blooded animal—rise of the external temperature causing rise of the internal temperature and increased elimination of CO_2, while a fall of the external temperature has the reverse effect.

It is still a subject of debate, what is the exact nature of the action of the central nervous system on the heat production of the body. It is evidently effected through the muscles, and, partly at all events, by means of muscular contractions. The increase of the tone in the muscles, and the general stringing up of the body after a cold bath, are an example of this. If the cold be more severe, the reflex contractions are more pronounced, and take on a clonic character, as shivering and chattering A man too has recourse instinctively to muscular exercise to ward off the effects of extreme external cold. It has been thought however that the nervous system has a distinct influence on the thermogenic properties of muscles apart from its action in producing muscular contraction; and that nervous impulses may call forth chemical changes in the muscle which give rise to heat and heat only. This view is supported by several phenomena, such as the increased production of heat in fevers, accompanied by a rapid wasting of the muscles, although the muscular tone in these cases is depressed rather than heightened. If the anterior part of the corpus striatum be pricked or stimulated, the animal suffers from pyrexia or rise of internal temperature for a day or two; and this rise is accompanied by increased elimination of CO_2 and production of heat. No special motor pheromena are observed in these experiments, and it has therefore been concluded that the increased heat production is due to a direct thermogenic action of the injury.

Regulation of Heat Loss

Far more important however than the regulation of the temperature by the production, is the regulation by the loss of heat. The channels of loss of heat may be classified as follows:

1. By the urine and fæces. In the warming of the food and drink taken into the body, there must be a certain abstraction of heat from the tissue surrounding the alimentary canal, though this heat is not lost to the body till the warmed urine and fæces leave it. The amount lost in this way has been calculated to be about 3 per cent. of the total heat loss.

2. By the inspired air. The inspired air is taken in at the temperature of the surrounding atmosphere, and contains only a small amount of aqueous vapour. The expired air has a temperature of about one degree lower than the body temperature, and is saturated with watery vapour. Heat is therefore lost in respiration in two ways: 1st, in warming the inspired air, and 2nd, in the evaporation of large quantities of water These two sources of loss constitute about 20 per cent. of the total heat loss.

3. By the skin. Here again the loss of heat is effected in two ways. 1st. By radiation and convection. By these means an interchange of heat takes place between the surface of the body and surrounding objects, tending to cool the body under ordinary circumstances when the external temperature is below 98·4° F., or 37° C., or to warm the body when the external temperature is higher than this, as during the hot season in the tropics or in a Turkish bath. The amount of interchange of heat between two bodies is directly proportionate to the difference of temperature between them. Thus the warmer the surface of the body in comparison with that of surrounding objects, the greater will be the amount of heat interchange, which in this case implies a loss of heat to the body. Since very little heat is generated in the skin itself, its temperature is intimately dependent on the amount of blood flowing through it, and this in its turn on the condition of the blood-vessels of the skin. When these are dilated, there is a constant supply of warm blood from the deeper parts of the body to the skin, which therefore is kept warm and feels warm, both subjectively and objectively. Hence dilatation of the blood-vessels of the skin, under normal circumstances, brings about increased loss of heat. If, on the other hand, the vessels are constricted, the small amount of blood supplied to the skin rapidly becomes cooled, and the skin is also cool, and the loss of heat small.

2nd. By the evaporation of the sweat. In the conversion of water into watery vapour a large amount of heat becomes latent. This principle is made use of in making ice, or in cooling a bottle of water by surrounding it with damp cloths which are exposed to a draught of air to facilitate evaporation. If the secretion of sweat is small it evaporates as it is secreted, and the skin remains dry. This is spoken of as insensible perspiration. If the secretion be very copious it may be formed faster than it can evaporate, and appears on the skin as drops of sensible perspiration. The formation of sensible perspiration depends then on two factors—the amount of sweat secreted, and the rapidity of evaporation, which latter again is dependent on the amount of saturation of the surrounding atmosphere with watery vapour.

The loss of heat by the skin amounts to about 77 per cent. of the total heat loss, and is therefore the most important of all the channels for the discharge of heat. The regulation of the total heat loss is also effected chiefly by changes in the loss through the skin. The nervous channels by which this is carried out are the vaso-motor and the sweat nerves. If the external temperature be below that of the body, the loss by radiation and convection may be sufficient to get rid of the excess of heat produced. If however the external temperature be higher than that of the body, radiation and convection will serve only to warm the body still further, and the sole loss of heat that can be effected is by the evaporation of sweat, which is accordingly under such circumstances secreted in large quantities.

Often, especially after severe muscular exercise, radiation and convection are not sufficient to carry off the excess of heat produced, and hence there is a copious secretion of sweat as well, even though the external temperature may be cool.

The evolution of heat is aided under such circumstances by two factors, viz. quickened and deepened respiration, by which a greater volume of air is warmed up to the body temperature at the expense of the body heat; and quickened heart-beat, by which more blood is driven through the dilated cutaneous vessels, and so a rapid loss of heat at the surface provided for.

In the dog, where there are no sweat-glands on the general skin, and the loss of heat by conduction and radiation is checked by the thick hairy coat, the quickening of respiration is the most important means for getting rid of the surplus heat produced in the body, and hence the panting and apparent distress of these animals in hot weather.

The extreme range of temperatures in a healthy man at rest is between 36·1° C. and 37·8° C.

So perfect is the adaptation of the heat loss to the heat production, that a man may travel from the poles to the equator, may eat or fast, take exercise or rest, without causing any lasting alteration in his temperature of 1° C., though violent exercise may induce in many individuals a temporary rise of temperature of 2° C.

The temperature of man, which varies from 97·8° F. to 98·4° F., undergoes certain diurnal variations, which are important, since they are reproduced in an exaggerated form in many fevers. The temperature is lowest between 2 and 4 a.m., and highest in the afternoon between 4 and 6 p.m.

SECTION 6

THE NORMAL DIET OF MAN

To maintain a man in perfect health it is necessary that his food shall contain examples of the five different sorts of foodstuffs—proteins, carbohydrates, fats, salts, and water. The first three classes serve as sources of energy to the body. Salts and water are equally necessary, although they cannot serve as sources of energy.

Water forms an integral part of all living protoplasm; and the phenomena of life, even in the lowest organisms, are dependent on an adequate supply of this substance. Apart from its function as a constituent of protoplasm, it is also essential as a medium for carrying the foodstuffs to the tissues, and the waste products from the tissues and out of the body. We have seen that water, in being discharged from the body, has two functions—as a solvent of the effete nitrogenous and other material contained in the urine, and as a powerful means by which the excess of heat produced in the body is dissipated. To supply this loss water must be a constituent of the foodstuffs.

The exact part played by salts in the body we do not know, although it has already been shown that the presence of calcium salts is a necessary condition for two physiological phenomena—the clotting of milk and of blood. It has been shown moreover that a frog's heart will go on beating for many hours if fed with a solution containing phosphates and chlorides of potassium, sodium, and calcium, although, if any one of these salts be absent, the heart soon comes to a standstill. Of the salts present in the body and taken in with the food, sodium chloride forms the largest quantity. The presence of potassium and phosphates however seems to be of more importance in the active phenomena of protoplasm, since these are found in largest proportions in organs consisting chiefly of cells with very little interstitial substance. It will be remembered too that potassium and phosphoric acid are the leading base and acid present in muscle and in blood-corpuscles. An animal, if fed on a diet free from salts, dies almost as quickly as an animal that is starved.

At an early period of life the human animal, as all mammalia, is fed exclusively on milk, and the composition of milk agrees almost entirely with the ideal composition of the normal human diet, that has been worked out by numerous authorities as the result of many laborious experiments. Thus it has been found that a man may maintain himself in perfect health, neither gaining nor losing weight, on a diet consisting of—

Proteins	100 grms.
Fats	100 „
Carbohydrates	240 „
Salts and water	

In cow's milk we find that for every 100 grms. of protein we take in 107 grms. fat and 140 grms. carbohydrates.

In human milk, for every 100 grms. protein there are 170 grms. fat and 270 grms. carbohydrates.

The following table represents the average compositions of human and cow's milk :

	Human	Cow's
Caseinogen and lactalbumen	2	4
Fats	2 75	4
Lactose (sugar of milk)	5	4 4
Salts	0 25	0 6
Total solids	10	13
Water	90	87

Milk when fresh is slightly alkaline or neutral. On standing exposed to the air the lactose is converted by the agency of micro-organisms into lactic acid. The milk hence becomes sour, and the caseinogen is precipitated.

Human milk has a specific gravity of 1025 to 1035.

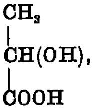
The proteins of milk consist of caseinogen and lactalbumen. Caseinogen, which forms by far the greater quantity, is a complex protein belonging to the group of phospho-proteins. From milk it may be precipitated by the addition of acetic acid or weak mineral acid. When purified it forms a snow-white powder, insoluble in water, but easily soluble in dilute alkaline solutions, such as soda, ammonia, lime, or baryta water. From these solutions it may be reprecipitated by neutralisation. The purified caseinogen when moist has the power of expelling CO_2 from certain carbonates, and is therefore looked upon as a weak acid. In the milk, caseinogen occurs in combination with calcium. Its power of clotting with rennet ferment has been already described (p. 323).

Lactalbumen, which resembles very closely serum albumen, is present only in traces in cow's milk, but in much more considerable quantities in human milk. The relatively smaller amount of caseinogen in human milk probably accounts for the fact that the clot produced by rennet in the latter is flocculent, and does not form a firm compact mass as in cow's milk.

Fats occur in milk in the form of minute droplets of various sizes. It is the presence of these which gives to milk its brilliant white appearance. If milk be allowed to stand they rise to the surface, forming the layer of cream. The droplets are probably prevented from running together by being surrounded with a protein envelope, or perhaps this is effected simply by the physical nature of the solution of caseinogen in which they are suspended. If cream be beaten or churned, this physical condition is overcome, and the fat droplets run together to form a mass known as butter. The fats of milk or butter consist of the glycerides of stearic, palmitic, and oleic acids, with traces of the glycerides of capric, caprylic, capronic, and butyric acids.

The carbohydrates are represented by lactose ($C_{12}H_{22}O_{11}$) or milk-sugar. This is much less soluble in water than cane-sugar, and is only faintly sweet. It reduces Fehling's solution, but does not reduce Barfoed's solution. It forms with phenylhydrazine an osazone which is fairly soluble in water On boiling with dilute acids it takes up water and is converted into equal parts of dextrose and galactose:

$$C_{12}H_{22}O_{11} + H_2O = \underset{\text{Dextrose}}{C_6H_{12}O_6} + \underset{\text{Galactose}}{C_6H_{12}O_6}.$$

Under the influence of the lactic acid organism it is converted into lactic acid. $C_{12}H_{22}O_{11} + H_2O = 4C_3H_6O_3$. This lactic acid is, like the acid of muscle, an ethylidene lactic acid,  $\begin{array}{l}CH_3\\ |\\ CH(OH)\\ |\\ COOH\end{array}$, but, unlike this, is optically inactive. The souring of milk is due to this conversion of lactose into lactic acid.

The salts consist chiefly of the phosphates and chlorides of sodium, potassium, calcium, and magnesium. Of these calcium is present in the largest quantities to supply the material needed for the rapidly growing bones of the young animal. The potassium occurs in far larger amount than the sodium, as would be expected from what has already been said concerning the part played by potassium in the functions of living protoplasm.

Milk also contains small traces of iron in combination with some protein body.

The food of the adult consists chiefly of meat, eggs, cereals, and green vegetables.

The following may be taken as an example of a complete diet (Waller):

		Carbon	Nitrogen
Foundation	1 pound bread	117 grms	5.5 grms.
	½ pound meat	34 ,,	7.5 ,,
	¼ pound fat	84 ,,	—
Accessories	1 pound potatoes	45 ,,	1.3 ,,
	½ pint milk	20 ,,	1.7 ,,
	¼ pound eggs	15 ,,	2 ,,
	⅛ pound cheese	20 ,,	3 ,,
		335	21

This diet is considerably more liberal than that given on p. 508.

Meat consists of several animal tissues. Muscular tissue forms the greater part of it, though it also contains white fibrous tissue in the connective tissue and aponeuroses, and some interstitial fat. There is also a greater or less quantity of fat surrounding the muscles. Meat in its most general sense therefore comprises proteins (myosin and albumen), fats, collagen or (in cooked meat) gelatin, and minute traces of carbohydrate, as glycogen or sugar.[1]

Eggs consist of two parts, the white and the yolk. The white is simply a solution of egg albumen, with a small amount of globulin and ovo-mucin, enclosed in delicate

---

[1] Lean beef contains in every 100 parts—

Proteins	18.36
Gelatiniferous substances	1.64
Fat	0.90
Extractives	0.90
Ash	1.30
Water	76.80

membranes. The yolk contains a peculiar phosphorised protein, vitellin, a large amount of fats, salts, and traces of sugar and iron. The latter, as in the case of milk, is present in a complex organic compound allied to the nucleo-proteins.

A hen's egg weighing 53 grms. (average weight) contains 31 grms. of white of egg (albumen and water with a small amount of globulin), 16 grms. of yolk, and 6 grms. of egg-shell. A man would have to eat twenty eggs a day in order to obtain the amount of protein given in the standard diet on p. 508.

The vegetable articles of diet are distinguished from the animal in containing a much larger proportion of indigestible material, chiefly consisting of cellulose. This also encloses much of the digestible portions of the vegetable, so that these also pass out in the fæces undigested. On this account a certain amount of vegetable food is of importance in the normal dietary, since the indigestible residue increases the bulk of the fæces, and aids the normal action of the bowels.

The cereals are the most important class of vegetable foodstuffs. They include wheat, barley, rye, oats, maize, and rice. Wheat-flour, out of which bread is made, contains proteins, carbohydrates, and a small amount of fat (less than 2 per cent.). The proteins, forming about 12 per cent., are two in number—a protein belonging to the class of globulins, soluble in 10 per cent. NaCl, and an albumose. On treatment of flour with water a change takes place in these proteins, and the flour becomes sticky and 'doughy.' In the dough two proteins are found—*gluten*, or vegetable fibrin, and a sticky body, *gleiadin*, which is soluble in alcohol, and gives the reactions of an albumose. The carbohydrates consist almost entirely of starch, which forms about 70 per cent. of wheat-flour.

Bread is made by moistening flour with water, so as to form dough. This is mixed with some dough which has been made previously, so that the diastase contained in the flour has had time to act on the starch, converting this into dextrin and maltose. The mixed doughs are then kneaded with a little yeast, and set in a warm place to 'rise.' By the action of the maltase of the yeast, the maltose is converted into dextrose, and this is decomposed by the yeast with the formation of alcohol and carbon dioxide. This latter forms little bubbles in the dough, causing it to swell up. The raised dough is then baked. In the latter process the starch, exposed to a temperature of 200° C. to 270° C., becomes partly converted into dextrin, and is therefore rendered soluble in water.

Green vegetables are chiefly valuable in the human dietary owing to the large proportion of salts and cellulose in them. Potatoes consist nearly entirely of starch, and contain very little protein. Hence to support life by this means alone very large amounts must be taken. It must be remembered that starch-grains are enclosed in a series of cellulose envelopes, and are therefore indigestible when raw. On boiling the starch-grains swell, rupturing these envelopes, and the opalescent semi-solution of starch thus formed is easily acted on by the digestive juices.

CHAPTER XII

THE DUCTLESS GLANDS

UNDER this title have been grouped a number of organs, the sole resemblance between which lies in the fact that we know very little about them. Since however they seem to exert important though obscure influences on the nutrition of the body, they may be fitly discussed after the chapter on metabolism. In many instances their functions seem to be to furnish an 'internal secretion' to the lymph or blood which leaves them. This is almost certainly the case with the thyroid gland, but the exact nature of the secretion or its action is in all cases very difficult to determine. It may act as an antitoxin to certain poisonous products of the normal activities of the tissues, or as a necessary physiological stimulus to the growth or the normal functions of one or a group of tissues.

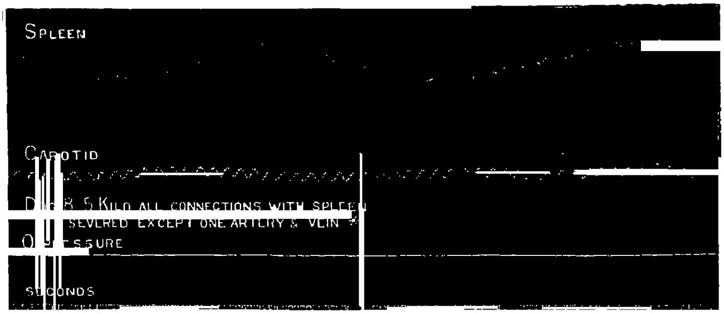
The chief ductless glands are the spleen, thyroid, thymus, and suprarenal capsules, but besides these, other glands, such as the pancreas, ovaries, testes, have been thought to influence the body by means of internal secretions. We have also to mention the small bodies of unknown function such as the pituitary body, the pineal body, the parathyroids, the carotid and coccygeal glands.

THE SPLEEN

This organ is similar in many respects to a lymphatic gland. It is formed of a framework of connective tissue and unstriated muscular fibres, in the interstices of which is contained the *splenic pulp*. This consists of a fine fibrillar network, on the fibrils of which lie endothelial cells. The meshes contain the cells of the splenic pulp, which are fairly large polygonal cells, and leucocytes. Just as in a lymphatic gland the cellular elements of the tissues are bathed by the lymph which flows through the gland, so in the spleen the walls of the capillaries become discontinuous, and the blood is poured out into the interstices of the tissue. The spleen is therefore the only tissue in the body where the blood comes in actual contact with the tissue-elements themselves. The blood from the splenic pulp is collected into large venous sinuses, which run along the trabeculæ to the hilum, where they unite to form the splenic vein. The arteries to the spleen are beset in their course along the trabeculæ with small nodules of lymphoid tissue, which are known as the Malpighian follicles.

It is evident that the blood must meet with considerable resistance in passing through the close meshwork of the splenic pulp. To ensure a constant circulation through the

Fig. 224



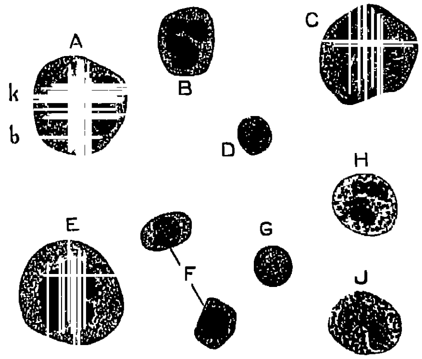
Plethysmographic tracing of spleen (upper curve) from dog, showing the spontaneous contractions of this organ (reduced from a tracing by Schafer)

gland, we find that the muscular tissue of the capsule an trabeculæ has the property of rhythmic contraction. If th spleen be enclosed in a plethysmograph, or splenic oncometer and its volume be recorded by connecting this with th oncograph, it will be seen that it is subject to a series o large, slow variations, each contraction and expansion lasting about a minute, and recurring with great regularit (Fig. 224) Superposed on these large waves are seen th smaller undulations due to the respiratory variations of th blood-pressure, and on these again the little excursion corresponding to each heart-beat. The contractile power o the spleen is under the control of the nervous system, an a rapid contraction may be induced by stimulation of the splanchnic nerves.

Functions of the Spleen

The structure of this organ suggests that the splenic cells must exercise a constant influence on the blood which surrounds them, and that this influence is not purely of a chemical nature. In the liver and kidneys, which exercise so powerful an effect on the composition of the blood passing through them, the proper cells of the organs are separated from the blood-stream by the capillary wall. Microscopic examination of the cells of the splenic pulp shows us that these are full of particles of brown pigments or fragments of red corpuscles (Fig. 225). In many cases of infectious disease, such as recurrent fever, the splenic cells are observed towards the end of the attack to be full of the organism—spirillum—which is the cause of the disease. In fact, these cells are so arranged that they can take up solid particles held in suspension in the blood-plasma. We must indeed look upon the spleen as the great blood-filter, purifying the blood in its passage by taking up particles of foreign matter and effete red corpuscles. The process of

FIG. 225



Cells from a scraping of the spleen (Kolliker). A, splenic pulp cell containing red blood-corpuscles, b (k = nucleus), B, leucocyte with polymorphous nucleus, C, pulp-cell containing disintegrated red corpuscles, D, lymphocyte, E, giant-cell, F, nucleated red corpuscles, G, normal red corpuscle, H, multinuclear leucocyte, J, eosinophile cell phagocytosis, which was described under Inflammation, is in the spleen a normal occurrence.

A function has also been assigned to the spleen in the formation of red blood-corpuscles, but the evidence is not sufficient to determine whether such a process occurs normally.

Chemical analysis of the spleen reveals the presence of a large number of what are called extractives, such as succinic, formic, butyric, and lactic acids, inosit, leucine, xanthine, hypoxanthine, and uric acid. There is also a protein allied to alkali-albumen, combined with iron, as well as several pigments probably derived from the hæmoglobin of the red corpuscles destroyed by the cells of the splenic pulp. The fact that, in cases where the spleen is pathologically enlarged as in leucocythæmia, the uric acid in the urine is largely increased, points to a connection between the spleen and the formation of uric acid in the body. The numerous extractives which are formed probably owe their origin to the destructive changes effected on the effete constituents of the blood by the agency of the splenic pulp-cells.

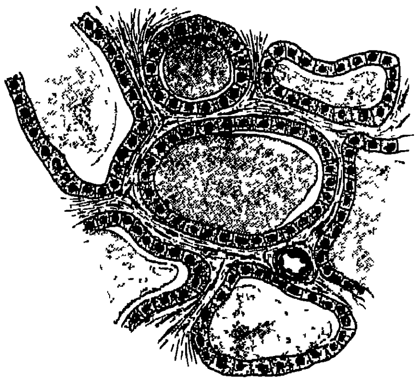
THE THYMUS GLAND

The thymus is a body situated in the anterior mediastinum; it is richly supplied with blood-vessels, and is composed of modified lymphoid tissue, which is peculiar in containing epithelial remnants known as Hassall's corpuscles, and derived from the epithelium of the branchial clefts of the embryo. It is only of importance in early life; it is relatively large in the fœtus, and increases in size during the first two years after birth. It afterwards atrophies, and in adult life is represented by a small collection of adipose tissue. Of its function we know nothing. It is supposed to be of importance in the formation of blood in the young animal. From the thymus a body can be extracted (tissue-fibrinogen) which, injected into the veins of an animal, causes intravascular clotting. This fact however does not throw any light on the normal functions of the gland, since a similar body may be extracted from almost any organ that is rich in cells.

THE THYROID GLAND

The thyroid was probably at one time in the history of the race a secreting gland in connection with the alimentary canal. In the developing animal it is formed, like the pancreas and liver, as an outgrowth from the fore-part of the alimentary canal. Long before the end of fœtal life however, its duct becomes obliterated, and each acinus becomes closed. In the adult it consists of two oval lateral lobes lying on each side of the upper part of the trachea and united across the front of this tube by a middle lobe or isthmus. Each lobe is made up of a number of vesicles of various sizes imbedded in connective tissue, which carries the blood-vessels, nerves, and lymphatic vessels of the gland. The vesicles are lined by a single layer of cubical epithelium and filled with a peculiar hyaline material known as the colloid substance (Fig. 226). In some cases this colloid material can be seen to extend between the lining cells into a neighbouring lymphatic vessel. The same path is often taken by artificial injections, so that it seems probable that the lymphatics may be regarded as the efferent ducts of the gland.

FIG. 226



Section of thyroid gland of dog. (Swale Vincent)

The colloid substance contains a nucleo-albumen, and a substance known as thyroiodin, owing to the fact that it contains iodine in organic combination with protein.

Although its primitive function of secretion is lost, it is still of the utmost importance in the metabolism of the body. If the thyroid gland be totally extirpated in young animals, the operation is followed after a short time by severe symptoms, consisting of fibrillar twitchings and spasms of the muscles, attended with weakness and stupor. These effects usually terminate in the death of the animal. In man it has been shown that a disease (myxœdema) occurring in adult life is dependent on the atrophy of this gland. The main symptoms of this disease are generally stupidity and slowness of speech of the individual, slow pulse, subnormal temperature, and a thickening of the subcutaneous tissues, so that the patient at first sight looks dropsical. All the processes of the body are slowed. The nitrogenous metabolism is diminished, as shown by the lessened outflow of urea; menstruation in women ceases, the hair falls out, and the skin becomes dry and harsh.

Cretinism is also associated with absence of the thyroid gland. A cretin remains a childish idiot all his life, and preserves his childish appearance. In these cases small fatty tumours are often found on each side of the neck just above the clavicle. We are absolutely unable to explain the connection of these manifold symptoms with the absence of the thyroid gland. There seems to be no doubt however that they are due to the *absence* in the body of some substance which is normally supplied by the activity of the thyroid gland, *i.e.* an internal secretion, since the symptoms produced by the extirpation or atrophy of the gland may be relieved by the administration of the fresh or dried glands of sheep. It is interesting to note that administration by the mouth is as effective as subcutaneous injection, showing that the active substance, whatever it may be, is easily absorbed by the stomach and is not destroyed by digestion.

In healthy individuals thyroid extract is found to increase the output of urea, by causing increased tissue waste. Hence it has been used as a remedy for obesity. Large doses cause increased frequency and force of the heart-beat, and it has been thought that the symptoms of exophthalmic goitre, in which an enlarged thyroid is associated with protrusion of the eyeballs and great acceleration of the heart, may be due to an excessive production of the specific secretion of the gland.

THE PARATHYROIDS

These are small oval or rounded bodies about 5 to 12 mm. long, situated near the hinder border of each lobe of the thyroid, and in some cases imbedded in the thyroid itself. They consist of elongated groups of polygonal cells, apparently epithelial, bound together by connective tissue, which also forms a capsule to the gland. They are well supplied with blood-vessels. Their mode of development as well as their functions is unknown. According to some authors they are at least as important for the normal life of the organism as the thyroid itself, and it has been suggested that the nervous symptoms (muscular twitchings and convulsions), which follow total extirpation of the thyroid in animals, are really due to the simultaneous removal of the parathyroids. According to this view, if the parathyroids were left intact, removal of the thyroid in animals would always give rise to a condition analogous to that of myxœdema in man It is probable, however, that the parathyroids represent merely immature thyroid tissue, and have therefore a similar function.

THE PITUITARY BODY

This is a small body filling up the sella turcica of the sphenoid bone. It consists of two lobes, a posterior of nervous tissue, derived from the floor of the third ventricle with which it is connected by the infundibulum, and a larger anterior lobe formed by an ingrowth of the epiblast of the buccal cavity. This lobe consists of alveoli lined with epithelium and sometimes containing a material resembling the colloid of the thyroid, as well as solid masses of epithelial cells, all enclosed and bound together by a vascular connective tissue. The functions of this body are unknown. Its deep protected position has so far militated against its successful extirpation. It has been found however that in a large proportion of the cases of *acromegaly* (a rare disease characterised by overgrowth of the bony tissues of the face and extremities) the pituitary has been the seat of sarcomatous enlargement. It is suggested therefore that this body secretes a substance which is essential in some way or other for the proper nutrition and growth of the bones. The posterior lobe has been shown to yield a substance having a marked diuretic effect.

The *pineal gland* represents the remains of a primitive dorsal invertebrate eye. So far as we know, it is at present only of historical interest.

THE SUPRARENAL CAPSULES

These are small triangular bodies situated one above each kidney. They consist of cortex and medulla, the cortex composed of groups and columns of closely packed polygonal cells, while the cells of the medulla are more irregular in shape with a reticular arrangement. The medulla presents the openings of a number of large veins. Its cells contain a substance which stains brown with chromic acid and its salts.

Here again pathology has taught us more than physiological research. The disorder known as Addison's disease, and distinguished by the three cardinal symptoms of extreme weakness, vomiting, and pigmentation of the skin (which acquires a bronzed colour), was recognised by its discoverer to be due to atrophy of the suprarenal capsules. The explanations, which were formerly brought forward of the connection of these phenomena with the extirpation or destruction of the capsules, may be classified into chemical and nervous. The suprarenals have a twofold origin, their medullary part being derived from the sympathetic nervous system, and their cortical part from the surrounding mesoblast. The supporters of the chemical theory based their views on the fact that derivatives of hæmoglobin are to be found in these organs, and they therefore looked upon them as chemical depôts for the removal or destruction of the waste pigmentary products. Retention of these in the blood gave rise to poisoning symptoms, and to deposition of pigment in the skin. As upholding the function of these bodies in influencing nutrition through the nervous system, widespread degenerations in the central nervous system were described after their extirpation in animals. Subsequent investigations however have failed to confirm these results.

It seems more probable that the suprarenals, in part at any rate, owe their importance to the production of an internal secretion, which they pour into the blood bathing their cells. From the medulla of the suprarenal glands a substance, *adrenalin*, can be extracted which in minimal doses produces most marked effects. The chief results of the injection of this substance are marked rise of blood-pressure, due to constriction of all the arterioles of the body, and increased strength of the heart-beats. The active principle is not a protein, but is diffusible. It is a derivative of pyrocatechin, from which body it may be prepared synthetically (Dakin). It acts on nearly all muscular tissues, producing a lengthening of the contraction of skeletal muscle as well as the effects on heart and blood-vessels just described.

As a rule its injection causes great slowing of the heart-beats. If however the vagi be cut, this effect does not appear and the arterial pressure rises to two or three times its previous height. This effect is not abolished by previous section of the cord or the splanchnic nerves. This slowing of the heart can be probably regarded as directly occasioned by the great rise of blood-pressure, and only indirectly by the adrenalin. It is interesting to note that not all muscular tissues are thrown into action by adrenalin. In some cases the muscle may be inhibited and relaxed. In fact, in every case that has yet been investigated, the action of adrenalin on muscle is identical with that produced by stimulation of the *sympathetic* nerve supply to the tissue. Thus we may get, besides the effects already mentioned (viz. vasoconstriction and augmentation of heart-beat), dilatation of the pupil, erection of hairs, relaxation of intestinal wall and of bladder, flow of saliva, etc. This similarity of the effects of injection of adrenalin to those produced by general stimulation of the sympathetic is probably connected in some way with the development of the medulla of the suprarenals as an outgrowth of the sympathetic system itself.

It is supposed that this substance is being constantly produced and distributed over the body, its absence being responsible for the extreme prostration and muscular weakness which are so marked in Addison's disease. The pigmentation and vomiting of this disorder still remain to be accounted for, nor have we yet been able to assign any function to the cortex of the suprarenals, forming the greater bulk of these glands.

CHAPTER XIII

SPECIAL SENSES

SECTION 1

ON SENSATION IN GENERAL

WE must now consider the means by which the individual is made aware of the events occurring in the outside world, the means by which his environment acts upon him. This subject is comprised in the physiology of the special senses.

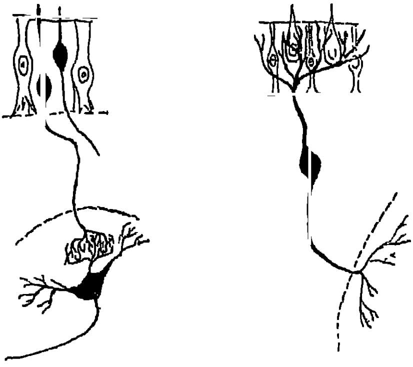
All the organs of special sense contain specially modified epithelial cells, derived from the epiblastic layer of the embryo, or processes of these cells. From the deeper side of these cells, processes or nerve-fibres grow into the central nervous system; these break up into fine arborisations of fibres which come into close contact with other cells or fibres, and so make functional connection with the nerve-tracts which serve as paths to the higher centres, or to the cells which preside over the movements of certain muscles.

In some cases, such as the olfactory mucous membrane (Fig. 227, A), the sensory cell lies close to the periphery, and is the immediate recipient of the physical stimulus which it has to transmute into a physiological nerve impulse.

In the auditory organ the special sense-cell seems to be represented by the bipolar cells of the spiral ganglion. These (Fig. 227, B) send one process towards the organ of Corti, where it terminates in fine filaments among the hair-cells, and one running in the auditory nerve towards the medulla.

In other cases the sensory cell may lie still further away from the sensory surface. Thus, in the skin, the sensory filaments ramifying in the epidermis represent the terminal arborisation of the process of a cell in a posterior root ganglion. This process joins by a T-shaped junction with another process which runs centralwards and terminates in fine filaments in the grey matter of the spinal cord and medulla (Fig. 228, A).

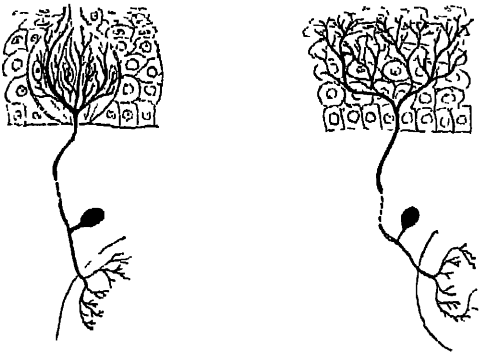
Fig 227



A Connections of olfactory cells with olfactory lobe
B Auditory sense-organs

The peripheral terminal filaments of these nerve-cells may either end freely among ordinary undifferentiated epithelial cells (as in Fig. 228, B), or may be closely applied to specially

Fig 228



A Connections of gustatory fibres. (Taste-bud)
B Nerve-ending in skin or corneal epithelium (probably pain-fibres).

modified epithelial cells. Such special sensory epithelium is found in the taste-buds (Fig 228, A) and in many parts of the skin (tactile corpuscles).

In every case a sensation, whether of heat, light, sound, or touch, is caused by some movement of molecules or masses occurring in the outside world, and the function of the special sense-organs is to be acted on by these movements and to convert them into a nerve impulse, which ascends an afferent nerve towards the spinal cord or brain. Arrived here, it gives rise to some form of reflex action, which may be unconscious or conscious. In the latter case we become aware of a *sensation* of light, heat, or sound, etc. Now it is found that if the nerve-fibres coming from a special sense-organ be stimulated artificially by electric shocks or in any other way, we get a sensation similar in kind to that which would occur if the sense-organ itself were stimulated in the normal way. Thus stimulation of the optic nerve gives rise to the sensation of light; of the auditory nerve, to one of sound; of the nerves of smell or taste, to these respective sensations. This fact, which has not been proved experimentally for all sensory nerves, is yet so general that it has been formulated as a law, known as Muller's law of specific irritability. This law merely states that every sensory nerve reacts to one form of stimulus and gives rise to one form of sensation only; that every sensory nerve, in fact, minds its own business.

Most important in connection with the physiology of the senses is the fact that in some cases we are able to *project* the stimulus, and recognise it as coming from an object at some distance from us. We can also *localise* the stimulus, and recognise what part of the body is being stimulated, or the position of the body in space from which the stimulus arises.

There is a certain proportionality between the strength of the stimulus and the intensity of the sensation produced; that is to say, a stronger stimulus will produce a stronger sensation. As the stimulus is increased, the amount of additional stimulus required to produce any appreciable increase of sensation is also increased. Thus we can distinguish the heavier of two weights—one of 39 oz., the other of 40 oz.; we cannot however between 39 lbs. and 39 lbs. 1 oz., but must add a whole pound to the 39 lbs. in order to appreciate a distinct difference. This fact is known as Weber's law, which runs thus: *The increase of stimulus which is required to produce distinct increase of sensation* *always bears the same ratio to the whole stimulus.* In the example above given this ratio is 1 to 40 (muscular sense). In the case of the pressure or tactile sense the ratio is 1 to 30. This law holds good only within certain limits, and fails when the stimuli are very strong.

Besides the five senses that are commonly recognised—of sight, hearing, touch, taste, and smell—physiologists reckon the senses of heat and cold, pain, the muscular sense, and the sense of equilibrium or static sense. The indefinite sensations of hunger, thirst, weariness, etc., defy accurate physiological analysis.

Section 2

CUTANEOUS SENSATIONS

The whole surface of the body is susceptible to stimuli, which may give rise to sensations of touch, heat, cold, or pain; and it seems probable that these different kinds of sensation are served by different sets of nerve-fibres. It is very difficult however to assign to each form of end-organ that has been distinguished by anatomists its proper function. Thus we find in the subcutaneous tissues the Pacinian corpuscles as well as the various kinds of end-bulbs, and the rich end-arborisations on the fibrous tissue bundles known as Ruffini's endings. In the papillary layer of the corium we find Meissner's corpuscles (the tactile corpuscles, Fig. 229). In the root-sheaths of the hairs there is a rich meshwork of nerve-fibrils, especially well marked in the tactile hairs. Finally in the epidermis there is the intra-epithelial plexus of non-medullated nerve-fibrils, as well as the fibres which end in connection with specially modified epithelial cells, the so-called tactile cells. Although we regard Meissner's corpuscles as essentially tactile, there is no doubt that the same functions must be served by the brushlike nerve-endings surrounding the hair follicles. On the other hand, the intra-epithelial plexus in the cornea must set up pain impulses, since these are the only sensations which result from stimulation of the cornea

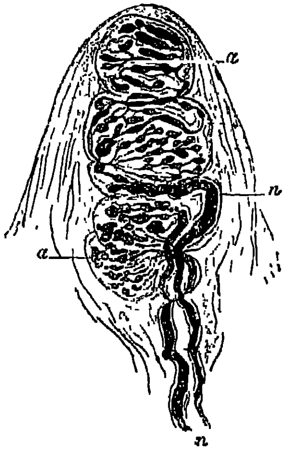
Tactile Sensations

By means of these sensations we are able to judge of the shape, size, and consistence of bodies in contact with the skin. Thus by feeling we can tell that a body is hard or soft, rough or smooth, single or multiple, etc. These conclusions however are not determined by the tactile sense alone, but are dependent on a number of other centripetal impulses, especially those concerned in the muscular sense or sense of movement.

On careful testing of the tactile sense, in minute spots over a given area of skin, it is found that the sensibility is not evenly distributed over the whole surface, but that the special tactile nerve-endings occur at definite spots, between which a strictly localised stimulus (as by the point of a hair) evokes no tactile sensation. These spots can also be mapped out by means of localised electrical stimulation, and it has been found that, using discontinuous stimuli, the sensation produced is also discontinuous so long as the rate of interruption of the current does not exceed 130 per second.

The tactile spots are especially marked round each hair follicle, but a few spots also occur between the hair follicles,

FIG. 229



Tactile corpuscle from a papilla of the skin (Ranvier) *n*, two nerve-fibres passing to the corpuscle, *a*, *a*, varicose ramifications of the axis-cylinders within the corpuscle.

and of course are thickly distributed over the palmar side of the hand and fingers.

Every tactile sensation has what is termed its local sign, *i.e.* we are able to localise the exact point at which the stimulus is applied to the skin. This power of localisation is intimately connected with the sense of movement and may be impaired by lesions affecting apparently only the efferent side of motor reactions. Intimately connected with the localisation is the power of discrimination of stimuli as single or multiple. Thus if two points tipped with cork, a quarter of an inch apart, be applied to the tongue, they are perceived as two points; applied to the skin of the back they give rise only to one sensation. The following table shows the distances which two points must be apart in order to cause two distinct sensations.

Tip of tongue	1 mm
Palmar surface of hand, terminal phalanx	2 „
Lip	9 „
Front of forearm	15 „
Forehead	23 „
Back of hand	30 „
Neck, back, arm, and thigh	50–70 „

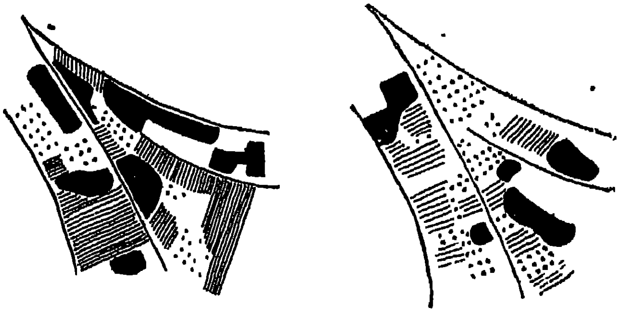
As we shall see later, tactile sensations are of immense importance in the reflex maintenance of equilibrium and the performance of co-ordinated movements.

Temperature Sense

Our subjective feeling of warmth or cold depends not on the temperature of the body itself, but on the temperature of the skin, where the special sense-organs are situated. It has been shown that in the skin there are two kinds of nerve-endings for temperature, which are excited respectively by heat or cold. Thus if a small metallic pencil, kept at body temperature by a stream of warm water through it, be moved gently over the skin, and the attention be directed on the sensations evoked, it will be found that while at some points the sensations are indifferent or merely tactile, at certain points the pencil may feel uncomfortably hot. The points where this is found to be the case are mapped out as heat spots. By using a cool pencil a series of cold spots may be mapped out in the same way, and it is found that this series does not coincide with the first. Fig. 230 shows the distribution of the heat and cold spots.

It is worthy of note that the cold spots are much more widely distributed than the warm spots, and this difference is especially marked in those portions of the body which are normally covered with clothes The hand is relatively insensitive to changes of temperature, and it may be observed as a general rule that in those regions where the tactile sense is best developed, the temperature sense is least developed. It is evidently of more importance to the organism that it should feel discomfort by a fall of temperature than that it should by a rise of temperature, as shown by the preponderance of social contrivances, sartorial and otherwise, for maintaining the body temperature over those for cooling the body. At a certain temperature varying in different parts of the body, the sensation of 'warm' undergoes a qualitative change and becomes that of 'hot,' and this change occurs some degrees lower than the temperature at which the threshold of pain is reached. It has been shown that, if the pencil used for testing the temperature sense is heated to 45° C. or over, it excites also the cold spots. To this excitation of cold spots is probably due the shudder which frequently occurs on entering a hot bath, and it seems that the feeling of 'hot' is really due to the simultaneous stimulation of both warm and cold spots. Thus if two adjacent spots of the skin be excited by a double pencil, half of which is warm and the other half cold, a sensation of heat is produced, whereas if the cold pencil be removed, the remaining sensation is only one of warmth.

Fig 230.



Cold spots Heat spots.

Heat and cold spots on part of palm of right hand The sensitive points are shaded, the black being more sensitive than the lined and these than the dotted parts The unshaded areas correspond to those parts where no special sensation was evoked (Goldscheider)

Pain

Over-excitation of the nerves of the skin, whether by cutting, electrical stimuli, excessive heat or cold, produces a sensation of pain. Hence it has been thought that pain is merely an hypertrophied tactile or temperature sensation, but there are arguments which tend to show that pain is a distinct sense, and subserved by a distinct set of nerve-fibres. Many cases of disease occur in which the patient can feel the slightest touch, but is quite insensitive to pain. In other cases, in which the tactile sense is deficient, the pain sense may be exalted. We can moreover map out on the surface of the skin pain spots similar to the heat and cold spots mentioned above. In certain regions of the body only one or more of these sensations may be present. Thus the surface of the cornea is sensitive only to painful impressions, that of the glans penis only to sensations of pain and cold, ordinary tactile and heat sensations being almost entirely absent.

Direct stimulation of the trunk of a nerve going to the skin gives rise only to a sensation of pain, whatever may be the nature of the stimulus. Thus plunging the elbow into a freezing mixture excites the ulnar nerve, and causes a sensation of pain which is referred to the ring and little fingers.

SECTION 3

SENSATIONS OF MOVEMENT AND POSITION

Under the above heading we may group a number of sensations which arise in special sense-organs in various parts of our body, in consequence of changes in these parts themselves, and are not directly occasioned by stimuli, arriving at the surface of the body from without. As examples we may mention those sensations by which we are able to tell the position in space of our body, and the relative position of its various parts, besides the extent, force, and direction of movements of any part, whether passive or active. Although in themselves indistinct and difficult of analysis, these sensations are of the utmost importance in qualifying other sensations, especially those of touch and sight, and in imparting to these sensations the properties which lead us to infer the position and extension in space of the object from which the stimuli arise.

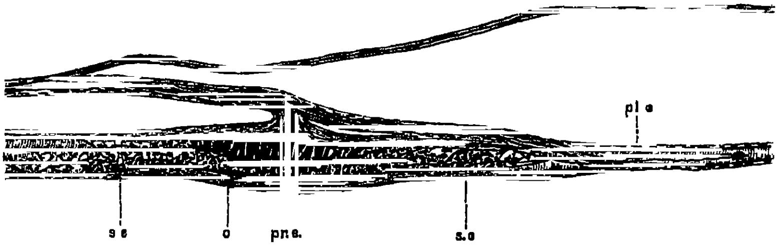
These sensations may be divided into two main groups—the muscular sense and the static sense.

Muscular Sensations

This term is applied to those sensations by which we know the position of our limbs, the extent to and the force with which they have been moved. Many authors have ascribed an important part in this knowledge to the so-called sense of innervation, *i.e.* a sense of the actual energy which is being discharged from the motor cells of the central nervous system to the muscles, and have thought that when we raise a weight we judge of its amount, not by the degree of stretching of the muscle or pressure on sensory nerves in the muscle, but by the amount of force we voluntarily put out to raise the weight. The fact however that we can judge of weights, when the muscles are made to contract by electrical stimuli and not by voluntary impulses, shows that this sense is in large part, if not entirely, peripheral. It is however very complex in nature and is served by a whole array of different end-organs in the skin, joints, tendons, and muscles. The muscles themselves are known to be well supplied with afferent nerves. Stimulation of the central end of a muscular nerve may reflexly excite or inhibit movements of other muscles. Sherrington has shown that, after section of the motor roots, over one-third of the fibres in a muscular nerve remain undegenerated, proving their connection with the posterior root ganglia. The sensory nerve-endings in the muscle are represented partly by the tendon nerve-endings, and partly by the muscle-spindles.

The former are richly branched end-arborisations of nerve-fibres on the surface of the tendon bundles. The muscle-spindles consist of one or more muscle-fibres, often continuous with normal fibres, enclosed in a sheath composed of several layers of fibrous tissue with intervening lymph-spaces. One or more nerve-fibres pierce this sheath and, after making many spiral turns round the muscle-fibres, branch freely and terminate in little knobs on the surface of the fibres. The cross-striation of the muscle-fibres within the spindle is but faintly marked. It is evident that the continuity of these sense-organs with the contracting muscle ensures in the best possible way that the organs should be affected by the slightest change of tension of the contracting muscle, and should transmit information of the state of tension to the central nervous system.

FIG. 231



A neuro-muscular spindle of the cat (Ruffini) *c*, capsule; *pr e*, primary ending, *s e*, secondary ending, *pl e*, plate ending (all these are probably sensory in function)

These organs, together with the special nerve-endings found on the tendons, are of importance in judging and controlling the force and extent of active movements. On the other hand our judgment of passive movements is largely determined by afferent impulses which arise in the sensory organs of the joints. It is evident that our sensations of resistance, and therefore our whole conception of force, power, and effort, are dependent on the tension of contracting muscles and on the muscular sensations thereby evoked.

Our knowledge of the position of our limbs depends chiefly on the complex of sensations which arise in the end-organs of the skin and subcutaneous tissue and the joints. Muscular sensations appear here to play but a subordinate part.

We shall later on have to refer to the importance of these afferent impulses for the carrying out of normal movements. We need here only mention that, in the absence of guiding afferent impulses, no co-ordinated muscular contractions are possible. Thus disease of the sensory nerves of the muscles of the legs or of the afferent tracts of the spinal roots and cord, such as occurs in tabes dorsalis, gives rise to the well-known ataxy, in which there is an entire absence of co-ordination between the contractions of the different muscles of the lower extremities. In walking, the leg is first raised too high and is then brought down again on the ground with a jerk. In the later stages of the disease, inco-ordination is so marked that with the greatest effort the patient is unable to move himself along, the muscles contracting violently and in no regular sequence when he attempts to walk. If the posterior roots of the hind limbs of a dog be divided, he is at first unable to stand on his forelegs, and in trying to move forward simply drags the apparently paralysed limbs after him Later on the dog learns to walk normally, but in this case he has simply replaced the normal afferent impressions from skin, joints, and muscles by visual sensations If he be painted with luminous paint, and placed in a dark room where his visual sensations are absent, the paralysis in his hind limbs will be seen to be as marked as on the day succeeding the operation. In the same way division of the posterior roots of a fore-limb of a monkey causes paralysis of the limb which, for the finer movements of the hand and fingers, is permanent.

In the judgment of weights, cutaneous impressions take little part. It has been found that the smallest appreciable difference is about $\frac{1}{20}$ of the whole weight—a proportion which holds good in the case of the arm for all weights between 0 and 6,000 grams.

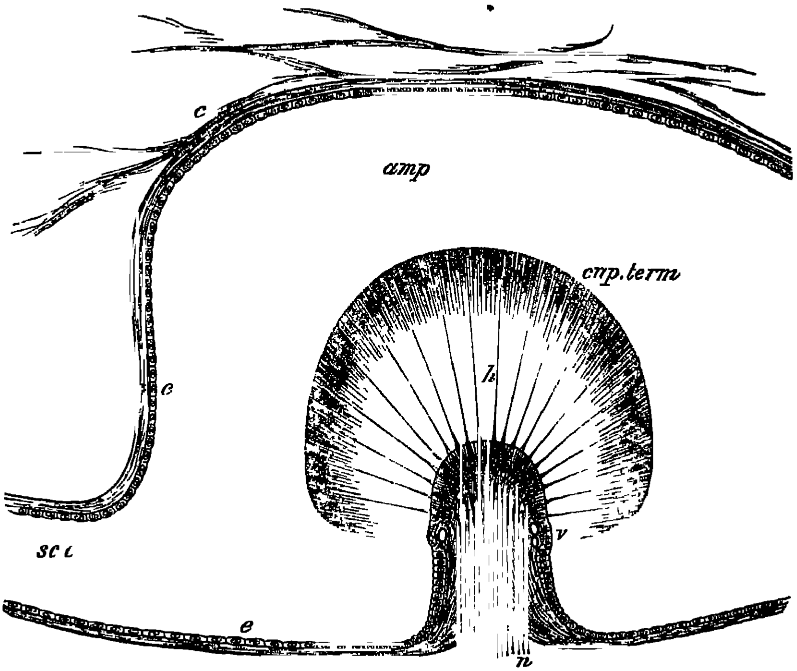
The Static Sense or Sense of Position

Deeply buried in the bones of the skull and in close relation to the auditory end-organ is a special sense-organ whose function it is to guide by its impulses the position of the head and therefore of the rest of the body, and by these impulses to arouse sensations by which we are informed of the position of the head as well as of the direction and extent of movements, active or passive, which the head may undergo. This sense-organ is formed by the endings of the vestibular nerve in the three semicircular canals and in the utricle and saccule of the internal ear. This, which is formed in the embryo by an involution of the epiblast and at first forms a simple sac lined with epithelium and lying under the surface of the skin, later becomes modified by outgrowths in various directions to form a complex membranous tube lined by epithelium and containing a fluid—the endolymph. This membranous labyrinth is contained within a bony tube—the osseous labyrinth, which it does not wholly fill, being separated from the bony wall over the greater part of its extent by a fluid—the perilymph. The bony labyrinth consists of a cavity—the vestibule, communicating by the fenestra ovalis with the tympanic cavity externally, and with the cochlea and auditory sense-organ anteriorly. The vestibule contains two sacs, the utricle and saccule, the latter being in communication with the spiral prolongation, which forms the canalis media of the cochlea and is connected with hearing. Behind the vestibule is in communication with the semicircular canals, three bony tubes lying in planes at right angles to one another and opening into the vestibule by five apertures, one aperture being common to two tubes. These canals are named respectively the external or horizontal, the anterior or superior vertical, and the posterior vertical canals. Within these bony tubes, and separated from them by the perilymph, are three membranous canals, each of which has a dilatation or ampulla at one end, and all communicate with the utricle; all these parts being developed from the primitive auditory vesicle In the ampullæ are situated the ultimate terminations of the vestibular division of the auditory nerve (Fig 282).

When these canals are injured definite disturbances of equilibrium are produced. Thus if in a pigeon the horizontal canal be divided, the head is thrown into a series of oscillations in a horizontal plane, which are intensified by section of the corresponding canal on the opposite side, so that the animal may fall down.

After section of the posterior vertical canals the forced movements are in a vertical plane, and the animal tends to turn somersaults head over heels. After section of the superior vertical canals the movements are still in a vertical plane, and the animal tends to turn somersaults backwards. After destruction of all the canals on both sides the disturbances of equilibrium are most pronounced and complicated. The animal can neither stand nor fly, nor maintain any fixed attitude, but is constantly executing somersaults, and moving about so violently and incoherently that it is necessary to pad its cage to prevent it killing itself.

FIG 232



End-organ of vestibular nerve in ampulla of semicircular canal ('crista acoustica')

After some months these disorders gradually disappear, and the animal learns to guide its movements by sensations of touch and sight alone. But they are instantly brought back in all their severity if the eyes be bandaged so as to deprive the co-ordinating centres of the guiding visual sensations.

It will be noticed that the semicircular canals on each side are in three planes at right angles to one another, and it is probable that we learn the positive movements of our body with regard to the three dimensions of space by means of impressions from the ampullary endings of the vestibular nerve. These impressions are caused by the varying pressure of the endolymph on the ampullary dilatations of the semicircular canals.

Thus a sudden turning of the head from left to right will cause movement of endolymph towards, and therefore increased pressure on, the ampullary nerve-endings of the left horizontal canal, and movement of endolymph away from, and therefore diminished pressure on, the corresponding ampulla of the right side. In this way, for movement in any given plane, the two corresponding semicircular canals of the two sides are synergic, and unite in sending impulses which guide the equilibrating centres, and inform us of the position of our head in space. 'One canal can be affected by and transmit the sensation of rotation *about one axis in one direction only*, and for complete perception of rotation in any direction about any axis *six* semicircular canals are required in three pairs, each pair having its two canals parallel (in the same plane), and with their ampullæ turned opposite ways. Each pair would thus be sensitive to any rotation about a line at right angles to its plane or planes, the one canal being influenced by rotation in the one direction, the other by rotation in the opposite direction.'[1] The two horizontal canals are in the same plane, and the posterior vertical canal of one side is in the same plane as the superior vertical of the other (Fig. 233).

In the pigeon it is possible to cause a movement of fluid in any desired direction in one of the canals. For this purpose one bony canal is exposed and plugged in the middle of its course as a dentist stops a tooth. The bony wall is then

[1] Crum-Brown.

removed immediately in front of the stopping and a small tube fixed on the head by means of plaster of Paris, in such a position that a blast of air from a rubber-ball connected by a flexible tubing with the first tube can be directed on to the opening in the canal, so as to set up a current of endolymph in the membranous canal. It is found invariably that the animal responds to each mechanical stimulus produced in this way, with a movement in the head and eyes in the same direction as the current of endolymph, and in the same plane as the semicircular canal involved.

These reflex movements of head and eyes are the invariable result of movements set up in the endolymph, and occur equally well in the absence of the cerebral hemispheres. If an animal or man be placed on a turntable and rotated, his first tendency will be to turn his head and eyes in the opposite direction to that of rotation. If the rotation be continued, the endolymph gradually takes up the movement of the surrounding parts of the head, and if the eyes be closed, no movement of head or eyes is observed. If now the rotation be stopped, the endolymph will tend to go on moving, and the effect will be the same as if a movement of rotation were suddenly begun in the opposite direction Head and eyes will now be turned, without any voluntary impulse, in the direction of the previous rotation and in consciousness there will be an actual sensation of rotation in the opposite direction. This sensation is in opposition to the sensations derived from other parts,

Fig 233

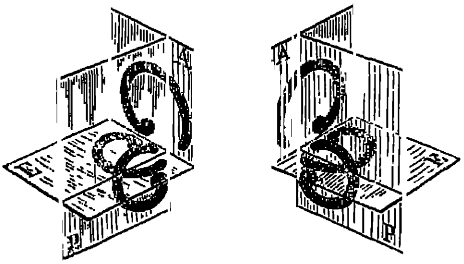


Diagram of semicircular canals to show their position in three planes at right angles to one another It will be seen that the two horizontal canals lie in the same plane (E), and that the superior vertical of one side (A) is in the same plane as the posterior vertical (P) of the other side (from Ewald) and hence the feeling of giddiness and the actual disorders of equilibrium which are its concomitants.

That this feeling of giddiness on rotation is due to impulses started in the semicircular canals is shown by the fact that, in a large number of deaf-mutes where these organs are imperfectly developed, it is impossible to produce giddiness and the associated eye-movements by passive rotation

It was mentioned above that, after destruction of the semicircular canals on both sides, the animal learns to guide its movements by sensations of touch and sight alone. This compensation depends however on the integrity of that part of the central nervous system which is eminently teachable, viz. the cerebral hemispheres. If these be removed in a pigeon and later on the membranous labyrinth on each side destroyed, the disorders of equilibrium which are produced are permanent

The Function of the Otoliths

Both utricle and saccule possess special nerve-endings known as the *maculæ acousticæ.* These resemble the crista acustica of the semicircular canals in structure, being formed by an elevation in the tunica propria of the lining membrane, which is covered by columnar cells bearing long stiff tapering hairs and supported by thin bipolar sustentacular or fibre-cells. The hairs project into a mass of a soft mucus-like substance which has a number of calcareous particles (otoliths) imbedded in it.

It is evident that the incidence of the weight of the otoliths on the hairs of the macula will vary according to the position of the head. Since similar structures have been shown (in invertebrata) to be essential for the proper equilibration of the animal, it is thought that the 'otolith organ' is specially adapted for conveying a sense of position (static sense), while the semicircular canals are chiefly engaged in the initiation of impulses which inform the central nervous system of the extent and direction of rotatory movements involving the head.

SECTION 4

TASTE AND SMELL

By means of our sense of taste we distinguish certain qualities of soluble substances which are introduced into the mouth. By means of smell we determine the qualities of the air which passes through the upper air-passages. In many cases, as in the appreciation of flavours, both senses are employed, and the sensations are referred to qualities of the food or other substance in the mouth. When the sense of smell alone is involved, the sensations are *projected* as a rule outside the body, and in many lower animals must form a considerable part of the substratum on which the representation in consciousness of the external world is built up.

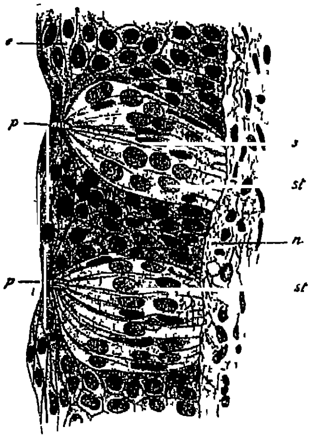
Together these senses represent the chemical sense, which is present to a greater or less degree in all living organisms, and which can generally be divided, as in the higher animals, into a sense regulating the intake of food, and a sense (corresponding to our projected sensations) which guides the relations of the organism to its environment. Thus the attraction of the antherozoids of ferns by the secretion of the female organ, the attraction of the plasmodium of myxomycetes by dead leaves and its repulsion by quinine, phenomena described under the name of positive and negative *chemiotaxis*, are exactly analogous to the attraction of a dog by a bitch in heat, or to the avoidance by ourselves of evil-smelling thoroughfares.

TASTE

The end-organs of the taste-nerves are represented by the *taste-buds* (Fig. 234), which are oval bodies consisting of medullary and cortical parts, the former being composed of columnar cells, the latter of thin fusiform cells, among which ramify the terminal fibres of the gustatory nerves. These occur scattered over the tongue and soft palate, but are especially numerous in the trenches round the circumvallate papillæ. A sapid substance to stimulate these organs must be in solution , hence quinine in powder is almost tasteless, owing to its slight solubility in neutral or alkaline fluids We distinguish four primitive taste-sensations, sweet, sour, bitter, and salt, and it is supposed that there are different nerve-fibres for each of these tastes. The reasons for this assumption are as follows:

a. The tongue is not equally sensitive at all points to all four tastes. Thus the back of the tongue is more sensitive to bitter, while the tip and sides of the tongue react more to sweet and acid tastes. Differences can be detected even between the circumvallate papillæ themselves; a mixture of quinine and sugar applied to one papilla may excite chiefly bitter taste, while with an adjacent papilla the sweet taste may predominate.

FIG. 234



Two taste-buds from the tongue. *e*, stratified epithelium; *p*, opening or pore of taste-bud; *s*, gustatory cells; *st*, sustentacular cells. (Kölliker.)

b. If the leaves of *Gymnema sylvestre* be chewed, the sensations of bitter and sweet are abolished, leaving intact the acid and salt tastes and also the general sensibility of the mucous membrane. On the other hand, cocaine abolishes general sensibility before it affects the sense of taste. Normally the effect of an acid is mixed with the biting sensation due to stimulation of nerves of general sensibility. After cocaine this pungent sensation is abolished and acid produces a very pure and intense acid taste.

When two taste-sensations are excited simultaneously, the total effect depends on the strength of the exciting stimuli. With weak stimuli, one taste may annul the other, so that the mixture used seems insipid. If the stimuli be then increased, as by increasing the strength of the solutions used (*e.g.* acid, quinine, sugar), a compound sensation results in which the component simple sensations are easily distinguishable.

Most of our so-called tastes are dependent on the sense of smell. Without this sense there would be very little difference between an onion and an apple. The epicure with a fine palate has really educated his sense of smell rather than of taste.

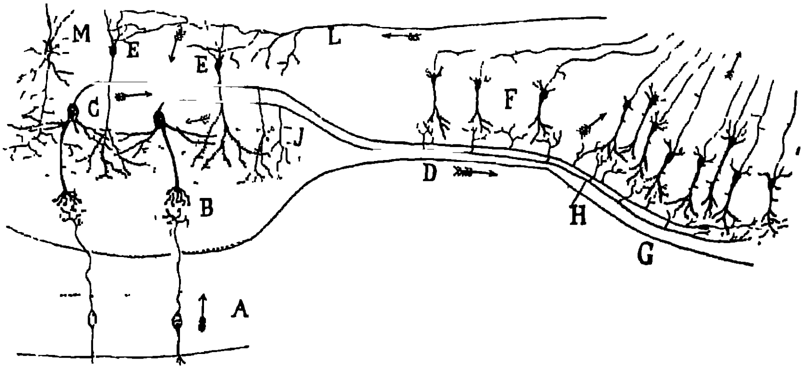
The nerves of taste are the glosso-pharyngeal, which supplies the back part of the tongue, and the lingual branch of the fifth nerve and the chorda tympani, which supply the front part. It is doubtful however whether there are really two nerves of taste. According to some authors the taste-fibres of the fifth nerve are derived from the glosso-pharyngeal nerve, perhaps reaching it through the tympanic plexus and chorda tympani nerve. Gowers has recorded a case however of complete unilateral loss of taste, in which there was a lesion destroying the roots of the fifth nerve, the glosso-pharyngeal being intact. It seems probable therefore that the fifth nerve (as it rises from the brain) is the only nerve of taste.

SMELL

The organ of smell is situated at the upper part of the nasal cavities. Here the mucous membrane covering the superior and middle turbinate bones and the corresponding part of the septum is different from that covering the rest of the nasal passages. Over the lower parts of the nasal cavities the mucous membrane is of the ordinary respiratory type, and is composed of ciliated columnar epithelium containing a number of goblet-cells. In the olfactory part however the epithelium is much thicker, of a yellow colour, and apparently composed of a layer of columnar cells resting on several layers of nuclei. These nuclei belong to the olfactory cells proper, true spindle-shaped nerve-cells with one process extending towards the mucus covering the free surface, while the other is continued along channels in the bone, and through the cribriform plate as one of the non-medullated olfactory nerve-fibres. These nerve-fibres dip into the olfactory lobes, where they terminate by a much-branched arborisation or end-basket in the so-called olfactory glomeruli, in close connection with a similarly branched dendrite of the large 'mitral' cells of the olfactory lobe. The axons from these latter carry the olfactory impulse towards the rest of the brain (Fig. 235). In the connective tissue basis (dermis) of the mucous membrane are a number of small mucous or serous glands (Bowman's glands) whose office it is to keep the surface of the membrane constantly moist.

A substance to excite a sense of smell must be in a gaseous condition, although before affecting the olfactory terminations it must be dissolved by the fluid bathing the nerve terminations. If the nasal cavities be filled with rose water, not only is no smell perceived, but the sense is paralysed for some time afterwards. This result is probably due to the injurious effect of the water on the mucous membrane. It is said that if the nostrils be filled with normal salt solution containing odorous substances, a sensation of smell is excited, but in such experiments it is difficult to ensure that all the chinks and crannies of the olfactory passages are filled with the solution, so as to exclude the possibility of the sensation being excited in the ordinary way by diffusion into the air of these passages.

Fig 235



Schema of course of olfactory impulses (Ramón y Cajal) A, olfactory mucous membrane, B, olfactory glomeruli, C, mitral cells, E, granule cells, D, olfactory tract, L, centrifugal fibres.

The sensitiveness of the olfactory is much greater than that of the gustatory organ. Thus whereas we can barely taste 5 parts in 10 million of quinine, applied to the most sensitive part, the back of the tongue, we can perceive the odour of mercaptan when it is so diluted that 1 litre of air contains only 0·00000004 milligram of this substance.

No satisfactory classification of smells has yet been made. The following facts however tend to show that there are a number of primitive sensations of smell, as of other sensations:

(*a*) Certain individuals, whose olfactory sense is in other respects normal, have no power of distinguishing some odours. Thus one may be without the sense of smell for vanilla, another for violets, another for hydrocyanic acid.

(*b*) The olfactory sense is easily fatigued. If it be fatigued so as to be absolutely insensitive for one kind of smell, it is still normally excitable for other smells.

(*c*) It is possible by mixing odoriferous substances in certain proportions to annul absolutely their effect on the olfactory organ. Thus 4 grams of iodoform in 200 grams Peruvian balsam is almost odourless, and the same neutralisation of odours is obtained if the odour of each substance be allowed to act separately on each side by tubes inserted into each nostril.

Dehyd [illegible]

SECTION 5

HEARING

Sound is a sensation produced in our ears by vibrations occurring in surrounding bodies, and transmitted to them by the atmosphere

Sounds produced by a regular series of vibrations are musical tones, if the vibrations are quite irregular the effect is a noise In a musical tone we can distinguish three qualities, according to the character of the vibrations; these are pitch, loudness, and timbre or quality The pitch of a note depends on the number of vibrations per second A note of 400 vibrations is an octave higher than a note of 200 vibrations The loudness of a sound depends on the amplitude of vibration The timbre or quality is dependent on the presence with the fundamental tone of certain overtones or harmonics Thus if we strike a piano string, the fundamental note of which is 100 vibrations, we get superposed on this tone a series of notes whose vibration frequencies are 2, 3, 4, 5, 6, 7 hundred It is on the varying predominance of these overtones that the differences between the sounds of a given note produced severally by the organ, piano, trumpet, and violin depend

If we raise the damper of a piano and sing into it, it will be noticed that a large number of the strings go on vibrating This is due to the fact that every note in our voice is accompanied by overtones, and the piano strings pick out those overtones which correspond to them in vibration frequency (pitch); they are said to resonate Instead of piano strings we may use cylinders of different lengths as resonators, and by employing a battery of these resonators it is possible to analyse all manner of compound sounds

The organ of hearing may be considered as consisting of an accessory part and an essential part. The essential part is formed by the terminal expansion of the auditory nerve; the accessory part is constructed so as to bring the waves of sound to act on the end-organs.

The ear is divided anatomically into three parts; the external ear with the auditory meatus, the tympanum, and the internal ear. The external ear in the lower animals is fashioned so as to collect sound-waves from different directions , and to this end it is provided with muscles, and is very movable. This function in man is rudimentary, so that he can hear almost as well with his ear cut off as normally The meatus is separated from the tympanum by the drum of the ear, or membrana tympani. This is formed by a thin layer of fibrous tissue, covered with skin externally, and with mucous membrane of the tympanum internally. Attached to the point of its inner surface, and dragging it inwards, is the handle of the malleus. The attachment of this to the membrane is eccentric—an arrangement which is of great importance, since the membrane in this way is rendered aperiodic, *i.e.* it will vibrate with equal facility to any number of vibrations, and not pick out a particular note, as a drum that was equally stretched all round would do.

The cavity of the tympanum is connected in front with the pharynx by means of the Eustachian tube. This is opened by each movement of swallowing, so that the pressure in the tympanum is kept equal to that of the outside air. If the Eustachian tube be blocked by disease, the air in the tympanum is absorbed, and the patient becomes deaf on that side. The inner wall of the tympanum presents in the dried skull two openings, the fenestra ovalis and the fenestra rotunda. The former opens into the vestibule of the internal ear and is normally closed by the base of the stapes. The fenestra rotunda leads into the scala tympani of the cochlea, and is closed in the fresh skull by an elastic membrane. Stretching across the tympanum, from the membrana tympani to the outer wall of the internal ear, is a chain of ossicles, the malleus, incus, and stapes. The base of the stapes is inserted into the fenestra ovalis, being joined to its margins by a membrane. This chain of bones acts as a system of levers, by which the vibrations of the tympanic membrane are transmitted to the fluid in the internal ear.

FIG 286

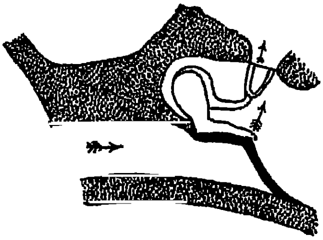


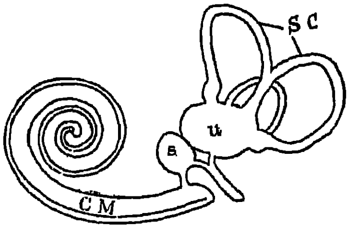
Diagram of auditory meatus, with tympanum and auditory ossicles

The excursion at the end of the lever formed by the stapes is only two-thirds of the excursion of the handle of the malleus, so that, in their transmission through the ossicles, the vibrations are diminished in extent but increased in force.

The tensor tympani muscle, which is attached to the handle of the malleus, serves by its contraction to draw this in, and to render the membrane more tense, and therefore more easily affected by high notes. The stapedius muscle, when it contracts, tilts the stapes backwards. Its use is unknown.

The internal ear consists essentially of a membranous sac, which is formed by an involution of the epithelium covering the surface of the embryo. In the course of development the sac, which is filled with a fluid called endolymph, becomes much modified in shape (Fig. 237), forming from before backwards the scala media of the cochlea, the saccule, the utricle, and the three semicircular canals. At certain parts of its inner surface thickenings of the epithelium occur, which become connected with the terminations of the auditory or eighth nerve. This 'membranous labyrinth' lies inside a casing of bone, from which it is separated by a layer of fluid called the perilymph. The osseous labyrinth is formed from before backwards by the cochlea, vestibule, and semicircular canals. The cochlea (Fig. 238) is a spiral tube of bone, 20 to 30 mm. long, divided by the scala media into two parts, the scala vestibuli and the scala tympani, which are continuous at the apex of the spiral (helicotrema). The scala media contains the essential part of the organ of hearing, which is called the organ of Corti (Fig. 239). This consists of a double row of stiff cells - the inner and outer rods of Corti, supporting on

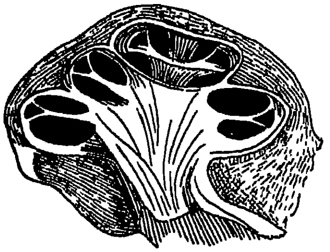
FIG 237



The membranous labyrinth C.M Canalis or scala media of the cochlea. S Saccule. U Utricle S C Semicircular canals.

each side one or three rows of *hair-cells*, which are connected with the terminations of the auditory nerve. The organ rests on the basilar membrane, which is composed of a number of elastic fibrils stretched in a radial direction from the central axis of the cochlea to the middle of the wall of

Fig 238

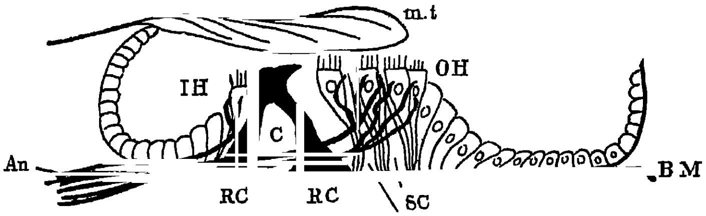


Vertical section through the cochlea.

the spiral. The length of the fibrils forming the basilar membrane increases from 0·041 mm. at the base to 0·495 mm. at the helicotrema.

Sound-waves falling on the ear are collected into the meatus, and strike the membrana tympani. The vibrations

Fig 239



Section through the end-organ of the auditory nerve in the cochlea (organ of Corti) B M Basilar membrane C Canal of Corti R C Rods of Corti IH and OH. Inner and outer hair-cells S C Sustentacular cells An Auditory nerve m.t Membrana tectoria

of the membrane thus produced are transmitted with diminished amplitude but increased force by the chain of ossicles to the fenestra ovalis, where they are communicated to the perilymph. The vibrations travel in the perilymph from the vestibule to the scala vestibuli, up the turns of the cochlea to the helicotrema, and then back again along the scala tympani, and end on the membrane closing in the fenestra rotunda, situated in the inner wall of the tympanum at the base of the scala tympani. Every movement inwards of the base of the stapes causes therefore a bulging of the membrane closing the fenestra rotunda. In their course the vibrations set the basilar membrane of the scala media into vibration, and in this way affect the hair-cells and the terminations of the auditory nerve.

The fact that in many cases we are able to resolve the compound sound into its simpler components, that a musician can name the notes forming a chord struck on the piano, shows that there must be some mechanism in the ear by which the sounds are analysed. This mechanism is supposed to be furnished by the basilar membrane. It is thought that the longer fibres near the apex of the cochlea vibrate only to low notes, and that the shorter fibres near the base of the cochlea vibrate only to high notes, and that when a chord is struck it sets into vibration fibres of the basilar membrane at different parts of the cochlea, each of which excites the hair-cells and auditory nerve-endings lying immediately on it, giving rise to a series of simple sensations.

The objection that has been raised to this theory of Helmholtz is that there is not enough difference between the lengths of the fibres of the basilar membranes at different points to account for the range of sounds which it is possible to perceive and analyse. It has therefore been suggested by Ewald that the whole basilar membrane vibrates, but with nodal points, so that a vibrating pattern is impressed on the nerve-endings, the position of the nodal points, and therefore the combination of fibres excited, differing with each tone or combination of tones.

Another theory would avoid the difficulty altogether by assuming that the basilar membrane vibrates as a whole like a telephone plate, and that the impulses ascending the whole auditory nerve differ in quality, reproducing physiologically the varying characters of the physical disturbances by which they were caused. Under this theory the whole process of analysis is relegated to the central nervous system.

Difficulties in the physiological theory of audition are represented by the so-called combination and difference tones. If two tuning-forks, one vibrating 200 and the other 250 times per second, be set vibrating, we hear not only the notes corresponding to these vibration frequencies but also two others, one of 50 vibrations per second (the *difference tone*) and one of 450 vibrations (the *combination tone*) Since it is said that these tones do not exist physically, we must conclude that the sensations corresponding to them are in some way excited in the auditory apparatus or central nervous system by the original two stimuli of 200 and 250 vibrations per second

The rate of vibration frequency, within which an audible note is produced, may extend from 16 to 40,000 vibrations per second, although in most people no sound is produced by vibration frequencies below 30 or above 30,000. According to Exner, two sounds following one another are perceived as distinct if the interval between them is not less than 0 002 second.

SECTION 6

VISION

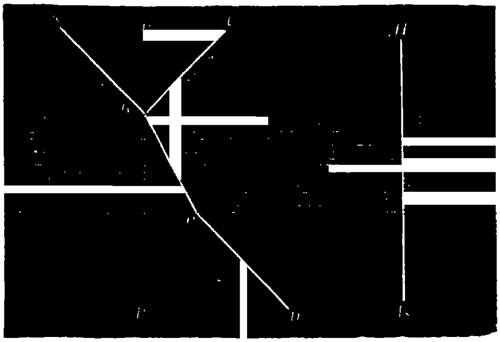
In treating of the functions of the eye, the organ of vision, we have to consider the essential part, the termination of the optic nerve or *retina*, and the accessory part, a series of dioptric mechanisms, arranged to form a perfect image of external objects on the retina.

Since the two eyes are generally employed together, we have also to discuss binocular vision; and lastly the cerebral processes engaged in the formation of visual sensations and judgments.

THE MANNER IN WHICH A DISTINCT IMAGE OF EXTERNAL OBJECTS IS FORMED ON THE RETINA

The eye may be compared to a photographic camera, the lens being represented by several refracting surfaces, the cornea, lens, and vitreous humour, and the sensitive plate on which the image is formed by the retina.

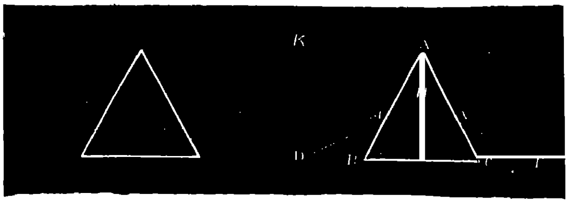
FIG 240



A ray of light when passing obliquely from a medium of low density (such as the air) to a medium of high density (such as water or glass) changes its course, being bent towards the perpendicular drawn to the surface separating the two media. On leaving the dense for a rarer medium it is bent once more away from the perpendicular.

Figs. 240 and 241 represent the course of a ray of light in passing through a plate of glass with parallel sides, and through a prism.

FIG 241



By means of a convex lens the rays of light from any one source may all be refracted so as to meet at a point. The point at which parallel rays of light (such as the sun's rays) meet is called the principal focus of the lens (Fig. 242).

FIG 242

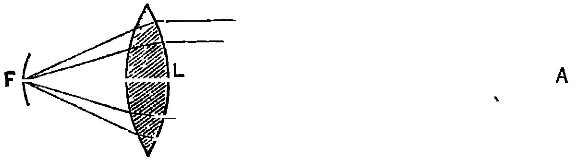
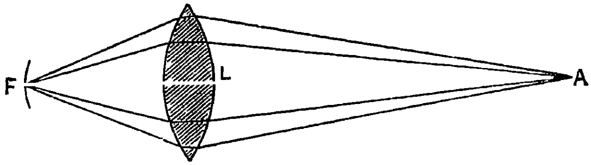


Diagram of the course of parallel rays through a biconvex lens, by which they are converged to the principal focus, F

If the origin of the rays be a point of light near the lens, so that the rays are not parallel, they are converged by the lens to a point (secondary focus) situated further away from the lens than the principal focus. The two points, the point whence the rays of light diverge and the point to which they converge, are called conjugate foci (Fig. 243).

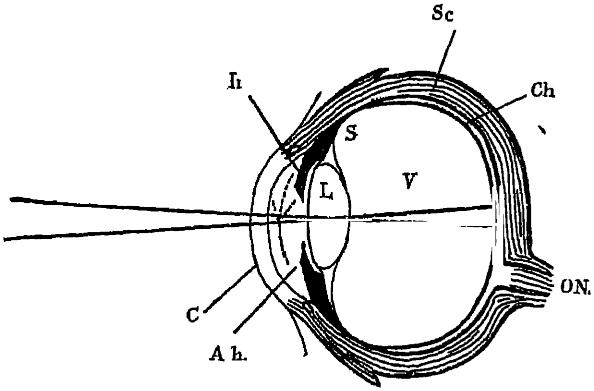
FIG 243



The rays of light from A converge on passing through the lens to the secondary focus, F F and A are conjugate foci.

In the eye there are several surfaces separating different media where refraction takes place (Fig. 244). Since the refractive index of the aqueous humour is almost equal to that of the cornea, we may reduce the refracting surfaces to three, viz.—

Fig 244



Section through eyeball to show refractive media. Sc. Sclerotic coat. Ch Choroid coat V. Vitreous humour L Lens S Suspensory ligament of lens ON. Optic nerve. C Cornea A h Aqueous humour Ir. Iris

Anterior surface of cornea,
Anterior surface of lens,
Posterior surface of lens;

and the refracting media to three—

Aqueous humour (or cornea),
Lens,
Vitreous humour.

These are so adapted in the normal eye that parallel rays falling on the cornea are converged to a focus at the yellow spot on the retina. This point therefore represents the principal focus of the eye. A line drawn from this point through the centre of the cornea is the optic axis of the eyeball.

The Mechanism of Accommodation

But we are able also to form a distinct image of near objects on the retina, and we notice that, when we turn our gaze from far to near objects, there is a distinct feeling of muscular effort in the eyes. There must then be some means by which the eye can be altered and arranged for focussing near objects. In a photographic camera the focus may be altered either by changing the lens, putting in one of greater or less curvature, or by altering the distance of the screen from the lens. The last method is obviously impracticable in the rigid eyeball, and we find that the act of focussing (or accommodating) for near objects is associated with a change in the curvature of the lens, which becomes more convex on its anterior surface.

This may be easily shown by means of the phakoscope (Fig. 245). This is simply a box, blackened inside, with holes at a, b, c, and d. At (a) is the observer's eye; at (b) the observed eye. Across the middle of (d) a wire is stretched.

Fig. 245.

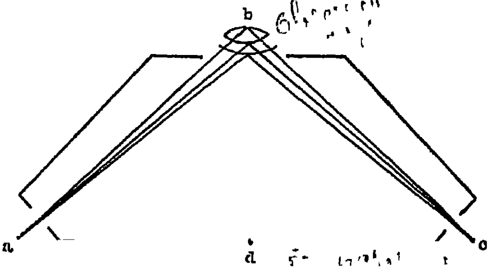


Diagram of phakoscope.

A candle is placed at (c). The observer at (a) then sees three reflections of the candle from the eye at (b) : 1 a bright erect image from the anterior surface of the cornea ; 2 a larger but dimmer erect image from the anterior surface of the lens ; and 3 a small very dim inverted image from the posterior surface of the lens. These images must be observed first when the eye at (b) is accommodated for a distant object, and then when it is accommodated for the wire stretched across the opening (d). It will be noticed that the change of accommodation from far to near objects is accompanied by a change in the second image (that from the anterior surface of the lens), which becomes smaller. The change in this image is more easily seen if the candle be made to throw two images on the eye by interposing a double prism at (c). Then, as the lens becomes more convex to accommodate for near objects, the two images of the candle reflected from its anterior surface approach one another (Fig. 240).

We must now inquire how this change in the shape of the lens is brought about.

By measuring the size of the image of the candle produced by the anterior surface of the lens, and knowing the size of the candle itself and the distance from the observed eye, it is possible to calculate the curvature of the lens in the living body.

The radius of curvature of a reflecting surface is given approximately by the following formula: $r = \frac{2\,a\,b}{c}$, where r is the radius of curvature, a the distance of the object, b the size of the image, and c the size of the object.

FIG 246

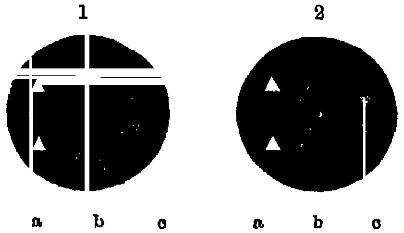


Diagram of reflected images from cornea and lens surfaces seen in phakoscope a From anterior surface of cornea b From anterior surface of lens c From posterior surface of lens. 1 During accommodation for distance 2. During accommodation for near objects

Of a, b, and c the only measurement which presents any difficulty is b, the size of the image. For this purpose therefore the ophthalmometer was devised by Helmholtz. The principle of this instrument may be gathered from the diagram (Fig 247) We may suppose that it is necessary to measure the line $a\,b$, which may be taken to represent an image reflected from the anterior surface of the cornea or lens If we look at this line through a plate of glass the plane of which is at right angles to our line of sight, no distortion of the line $a\,b$ takes place. If however the plate be placed obliquely, as at $g_1\ g_1$, there will be an apparent shifting of the line sideways to $c\ d$ In the ophthalmometer there are two glass discs, $g_1\ g_1$ and $g_2\ g_2$, one immediately over the other, so placed that the image $a\,b$ is looked at through the junction between the two plates. The plates are then turned, as in the diagram, until $a\,b$ appears as two distinct lines $e\,c$ and $c\,d$ just touching one another at c At this point each image of the line $a\,b$ has been shifted through one-half the length of $a\,b$. Knowing the thickness of the plates and their refractive index, it is easy to calculate, from the angle through which the plates have been turned, the apparent shifting of the line $a b$. This lateral movement amounts to $a c$, i e to $\frac{a b}{2}$, and we have merely to double this result in order to obtain the actual size of the image on the cornea or lens

If the lens be now cut out of the eye, it is found when freed from its supporting structures that the curvature of its anterior surface is much greater than it was before. It is evident that a pressure is normally exerted by some structure on the anterior surface of the lens, repressing its natural tendency to become convex. If we examine sections through the eye we find that this structure is the suspensory ligament of the lens.

FIG 247.

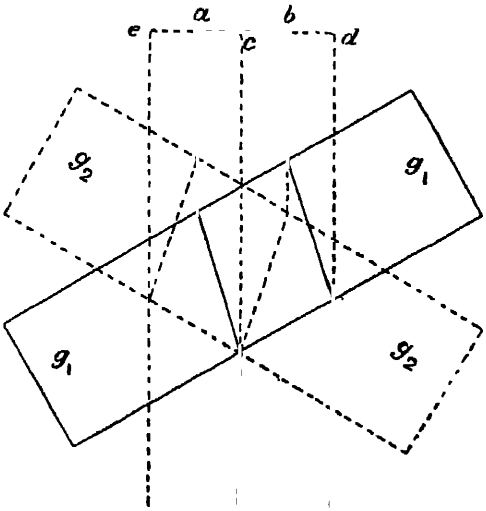


Diagram to illustrate principle of ophthalmometer (after Schenck)

The membrana hyaloidea of the vitreous is thickened in front and closely adherent to the ciliary processes. At the margin of the lens it divides, sending a thick tough expansion forwards to cover the anterior surface of the lens, and a thin expansion behind which separates the lens from the vitreous humour. The part of the membrane extending from the edge of the lens to the ciliary processes is the suspensory ligament. This ligament is normally on the stretch, and keeps the anterior surface of the lens nearly flat, so that the eye is accommodated for infinite distance. When the eye is to be accommodated for near objects the ciliary processes are pulled forwards and inwards by the contraction of the ciliary muscle, and so the suspensory ligament is relaxed and the front of the lens allowed to bulge forwards.

The ciliary muscle runs from the corneo-sclerotic junction, to be attached to the ciliary processes and front part of the choroid.

Accommodation is a voluntary action, although the ciliary muscle consists of unstriated fibres. Contraction is brought about through the intervention of the short ciliary nerves, which are derived from the third nerve. The nucleus of the third nerve is situated in the extreme hinder part of the third ventricle and the anterior part of the iter of Sylvius. The centre presiding over the movement of accommodation occupies the most anterior part of this nucleus.

Fig. 248.

Diagram showing change in lens during accommodation.
M. Ciliary muscle. *I.* Iris *L.* Lens *V* Vitreous humour.
A Aqueous humour *C* Cornea

Movements of the Iris

Accommodation for near objects is always associated with contraction of the iris, the function of which we must now consider. In an ordinary spherical biconvex lens the rays of light passing through the periphery of the lens come to a focus at a nearer point than the rays passing through the central parts. In this way a certain amount of blurring of an image is produced, which is spoken of as spherical aberration. This spherical aberration may be corrected in three possible ways:

1. By making the refractive index of the lens higher at its centre than at its circumference.

2. By making the curvature of the lens less near its circumference than at the centre.

3. By 'stopping out' the peripheral rays of light by means of a diaphragm.

The two latter methods are those used in most optical instruments. In the eye there is an attempt at all three, but the most important means is the third, the diaphragm being formed by the iris. This is a circular curtain with a hole in the middle, lying just on the anterior surface of the lens. Pigmented cells in it effectually stop out peripheral rays of light, and the size of the opening in it, the pupil, is controlled by the contraction or relaxation of a ring of unstriated muscular fibres situated near the margin of the pupil.

FIG 249

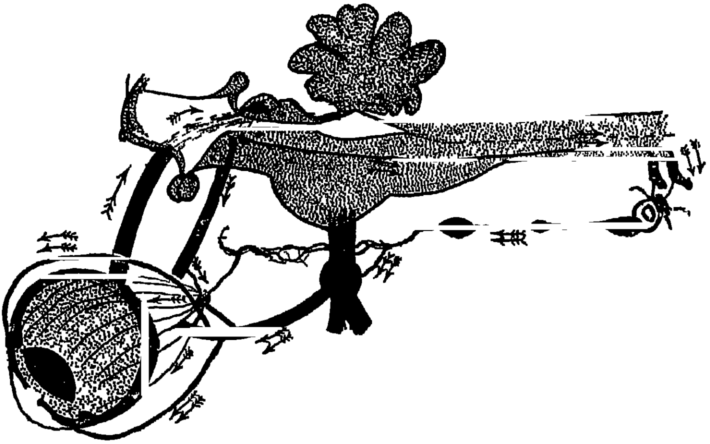


Diagram to show course of the impulses in the light reflex (marked by single arrows), and of those which, starting from the oculomotor nucleus, cause dilatation of the pupil (double arrows)

The iris has a twofold nerve-supply from the third nerve through the short ciliary nerves, and from the cervical sympathetic through the Gasserian ganglion, ophthalmic branch of the fifth, and the long ciliary nerves (Fig. 249). Stimulation of the third nerve causes contraction of the pupil. The centre for this movement is in the anterior part of the floor of the Sylvian iter, just behind the centre for accommodation. Stimulation of the cervical sympathetic produces dilatation of the pupil. The fibres serving this action leave the spinal cord by the second dorsal nerve, and pass up through the stellate ganglion in the cervical sympathetic. In this dilatation two processes are involved, viz. (1) the relaxation of the circular muscle-fibres, the *sphincter pupillæ*, and (2) the contraction of the radiating fibres which form the *dilatator pupillæ*.

Contraction of the pupil occurs under the following conditions:

1. Stimulation of the optic nerve by exposure of the eye to light, or by artificial means. In the higher mammals this is a crossed reflex, exposure of one eye to light causing contraction of both pupils.

2. Associated with movements of accommodation and convergence of the optic axes.

3. Various poisons, especially opium and physostigmin. The latter drug exerts a local influence on the iris, and can cause contraction of the pupil when all nerves to the eyeball are cut.

4. In sleep.

The pupil is dilated—

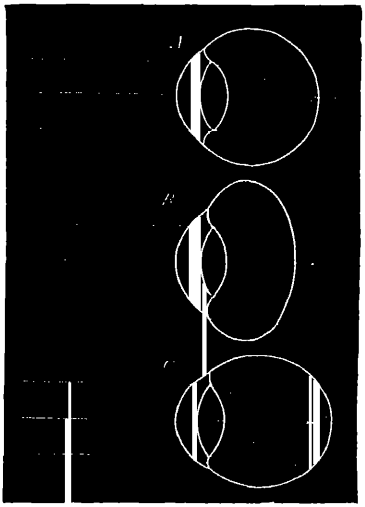
1. When the eye is removed from light.
2. Reflexly by strong stimulation of any sensory surface.
3. When accommodation is relaxed.
4. Under the influence of emotion, such as fear.
5. In the last stage of asphyxia.
6. In deep chloroform narcosis, and under the influence of atropin and other alkaloids derived from the solanaceous family. Atropin exerts a strong local influence on the iris. Stimulation of the third nerve has no power to constrict a pupil that is dilated fully by atropin.

Optical Defects of the Eye

Chromatic aberration.—Since blue rays are more refrangible than red rays, they are brought to a focus at a point nearer the lens than the red rays. This is the reason why with an ordinary magnifying glass we see a coloured fringe round the margins of the object. Chromatic aberration is corrected in optical instruments by using two different kinds of glass. In the eye it is uncorrected. Hence it is that a blue light and a red light at the same distance from the eye appear to be unequally distant; the red light, requiring greater accommodation than the blue, appears to be the nearer of the two. The error in most cases is so slight that we do not notice the chromatic fringes under normal circumstances.

Myopia.—The normal or emmetropic eye is so constructed that, when the ciliary muscle is relaxed, parallel rays are brought to a focus on the retina. If the eyeball be longer than usual, the parallel rays will come to a focus rather in front of the retina, so that it will be impossible for a clear image of distant objects to be formed on the retina. Objects at a certain small distance from the eye will be brought to a focus on the retina without any effort of accommodation. People with eyes of this description are said to be myopic or short-sighted. Under these circumstances concave spectacles are necessary, in order to form a distinct retinal image of distant objects.

FIG. 250.



Diagrams of course taken by parallel rays in entering normal (emmetropic) eye (*A*), hyperметropic eye (*B*), and myopic eye (*C*)

Long

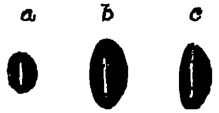
convex Spectacles

[illegible] eye - Short!

concave [illegible]

Hypermetropia.—If, on the other hand, the eyeball be too short in its antero-posterior diameter, the parallel rays entering the eye will come to a focus at a point behind the retina. In order that a distinct image may be formed, even of distant objects, it will be necessary to increase the curvature of the lens by contracting the ciliary muscle. Such eyes are hypermetropic or long-sighted.

FIG 251



Lens from human eye at different periods of life (Allen Thomson) *a*, at birth; *b*, adult, *c*, old age.

Presbyopia.—As old age comes on, the lens becomes more rigid, and loses more or less its tendency to become convex (Fig. 251). Hence the near limit of accommodation gets further and further with advancing age. Such a condition is not to be confused with long-sightedness; it is merely a defect in the power of accommodation, and not dependent on a structural defect of the eyeball. It is spoken of as presbyopia.

FIG 252

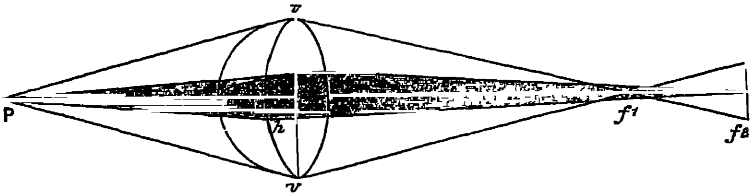


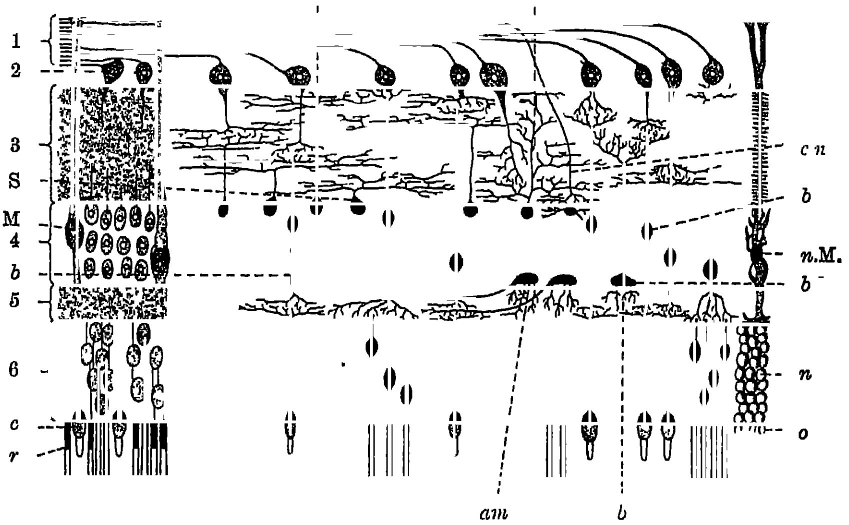
Diagram showing course of rays in an astigmatic eye (Waller) The curvature of the cornea is greater in the vertical meridian *v v v* than in the horizontal meridian *h h h* Hence the rays of light coming from the point P and passing through the vertical meridian come to a focus at f^1, while those through the horizontal meridian come to a focus at f^2 There is thus no point behind the cornea at which all the rays from P will come to a focus, and the image of the point must be blurred, being elongated in a horizontal direction at f^1, and in a vertical direction at f^2

Astigmatism.—The curvature of the vertical meridian of the cornea is usually greater than that of the horizontal meridian. The difference may be so great as to make it impossible for a definite image of a point of light to be formed on the retina, the rays diverging from the luminous point in the vertical plane (greater curvature) being brought to a focus sooner than those in a horizontal plane. To correct this defect it is necessary to use cylindrical glasses in order to make up for the lesser curvature of the cornea in this direction.

Retinal Changes involved in Vision

We have seen that, in nearly all sense-organs, the essential constituent is a bipolar nerve-cell having a peripheral process extending towards the surface and ending between the epithelial cells covering that surface, and a central process which runs towards the central nervous system, where it terminates in close contact with other nerve-cells.

Fig. 258.



Schema of retina (from Böhm and Davidoff after Cajal) 1, nerve-fibre layer, 2, ganglion-cell layer, 3, inner molecular layer; 4, inner nuclear layer, 5, outer molecular layer, 6, outer nuclear layer, *c*, cone, *r*, rod; *b*, bipolar cells, S, spongioblast, *am*, amacrine cell, *c n*, centrifugal nerve-fibre, M, fibre of Muller, *n* M, nucleus of fibre of Müller, *n*, neuroglia, *o*, outer limiting membrane

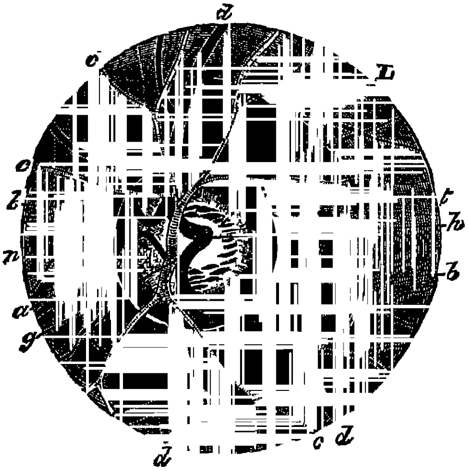
The retina however represents genetically not a simple sense-organ, but a whole lobe of the brain, and has therefore a much more complicated structure. It is composed of three separate relays of nerve-elements (neurons). These are—

(1) The rod and cone cells, with their nuclei (rod and cone and outer nuclear layers).

(2) Bipolar cells (inner nuclear layer).

(3) Ganglion cells (ganglion-cell layer), from which spring the axis-cylinders joining the nerve-fibre layer, and which run along the optic nerves and tracts to terminate in the region of the anterior corpus quadrigeminum. The functional connection between the processes of these three sets of nerve-cells takes place in the outer and inner molecular layers (Fig. 253).

Fig 254



Ophthalmoscopic view of fundus of eye, showing the optic disc, or point of entry of the optic nerve, with the retinal vessels branching from its centre.

Of these layers of the retina, the hindmost, the layer of rods and cones, represents the end-organ of vision; and therefore, for distinct vision to take place, the image of external objects must be formed on this layer. This is shown by the following facts:

a. The point of entry of the optic nerve, where the whole thickness of the retina is composed of nerve-fibres, is absolutely insensitive to light, and constitutes the 'blind spot' (Fig. 254).

b. At the macula lutea, where vision is most distinct, all the layers of the retina are diminished except the layer of rods and cones.

c. Purkinje's figures. If a strong light be focussed by means of a lens on the sclerotic just outside the cornea, and the eye be made to stare fixedly at a dull background, an arborescent image of the retinal vessels will appear on the background. On moving the illumination the image of the vessels will move in the same direction. Knowing the dimensions of the eyeball and the distance of the background from the eye, as well as the angle through which the light is moved and the apparent displacement of the image of the vessels, the distance of the percipient part of the retina behind the vessels may be calculated. This distance is found to correspond with the distance of the rod and cone layer from the retinal vessels, and hence this layer is taken to be the end-organ of vision.

FIG. 255.

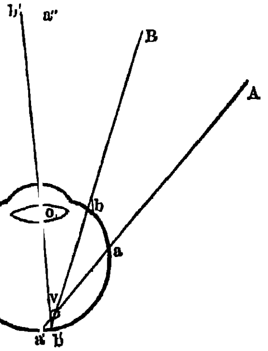
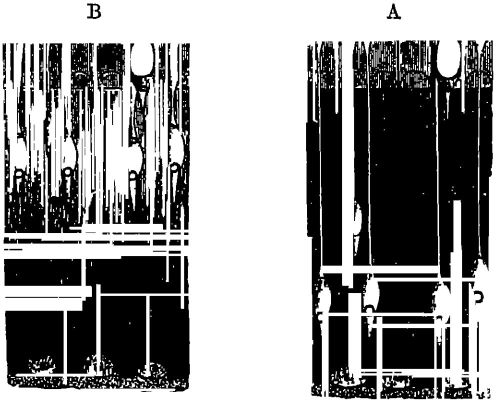


Diagram of the path of the rays of light in the formation of Purkinje's figures (v) represents a retinal vessel When this is illuminated from (A), a shadow is formed on the hinder layers of the retina at (a') This is projected along a line passing through the optic axis, and appears to come from a point (a'') on the wall On moving the light from (A) to (B), the image of the vessel appears to move from (a'') to (b'').

When light falls on the retina certain chemical and physical changes take place. These either originate or accompany the transmutation of the ether vibrations into the nerve-impulses, which ascend the optic nerve. If a frog that has been in the dark for some time be killed, an eye taken out bisected, and the retina removed and examined by a weak light, it will be found that this latter has a purplish-red colour. On microscopical examination this colour is seen to be confined to the outer limbs of the rods. After a very short exposure to diffuse daylight the colour disappears. The colouring matter (*rhodopsin*) may be dissolved out by means of a solution of bile salts. The purple-red solution thus formed also bleaches rapidly on exposure to light. By means of this rhodopsin, photographs or 'optograms' of external objects may be taken on the retina. The frog's eye which is cut out is placed in front of a window. After some time the eye is bisected and plunged into a 4 per cent. solution of alum, which fixes the optogram, and a permanent inverted picture of the window with its cross-bars is obtained on the retina.

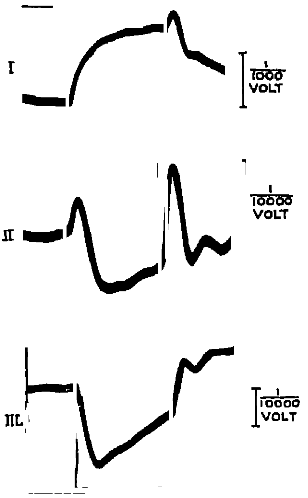
FIG 256



Sections of the frog's retina A, kept in the dark B, after exposure to light, showing retraction of the cones, and protrusion of the pigmented epithelium between the outer limbs of the rods (Engelmann)

If a retina, which has been bleached by exposure to light, be replaced on the pigment-layer lining the choroid, in a short time the colour will be restored. On examining sections through the retina it is found that, in those which have been exposed to light, the cells of the layer of pigmented epithelium send up fine processes full of pigmented granules between the outer limbs of the rods. In an eye which has been kept in the dark, on the other hand, the cells of the pigment-layer are quite flat, so that the front part of the retina, including the rods and cones, can be removed without any difficulty (Fig. 256). Thus the function of the pigmented epithelium is to supply visual purple to the outer limbs of the rods as fast as the pigment already there is bleached by light. It might be thought that this chemical change was the active agent in producing excitation of the optic nerve-fibres ; but the facts that in the fovea centralis, the region of most distinct vision, we find only cones which contain no visual purple, and that in certain birds there are no rods and no visual purple in the whole retina, show that this chemical process, interesting though it may be, is not essential for the conversion of light-waves into a nervous impulse.

Fig 257



Three types of retinal variation obtained on exposure to light (Waller) I, fresh retina. II, same retina after two hours III, same retina after twenty-four hours The black line at the lower border of each record marks the period of exposure to light

When light falls upon the retina the cones are retracted, and lie close upon the external limiting membrane , whereas in an eye that has been kept in the dark they extend down between the rods as far as the pigmented layer.

The falling of light on the retina is also accompanied by an electrical change, which may be regarded as analogous to the current of action in nerve.

The conditions in the retina are however rather more complicated. An eyeball of the frog led off from its anterior and posterior surfaces shows a current directed in the eyeball from behind forwards (the resting or demarcation current) On allowing light to fall into the eye this current after a delay of several seconds is markedly increased. On shutting off the light there is a momentary further increase and then diminution of the current to its resting value (Fig. 257, I). Waller interprets this change as showing a twofold process of disintegration and anabolism during stimulation by light—the anabolic effect however predominating so far as regards the changes affecting the galvanometer. On shutting off light, the dissimilative changes cease at once, the assimilative more slowly; hence the further positive variation On keeping the eyeball the positive variation gradually diminishes, so that, twenty-four hours after excision, exposure to light may cause a pure negative variation, succeeded by a slight positive effect when the light is shut off (Fig. 257, III).

ADAPTATION

The sensitiveness of the retina to light is continually altering according to the strength of the illumination. Thus, when we go from a brightly lighted place into a dark room, at first we are unable to distinguish objects. The pupil dilates widely from the absence of stimulation. In a short time, however, 'adaptation' occurs, and we may be able to see quite clearly. When the eyes are removed from light to darkness, within the first ten minutes the sensitiveness of the retina is increased twenty-five times, and at the end of two hours is as much as thirty-five times as great as it was in full illumination. This adaptation is *retinal* and not conditioned by changes in the size of the pupil, which after the first reaction to the change of illumination resumes its normal size.

In the 'dark-adapted' eye (*i.e.* one that has been removed from all sources of illumination for a considerable time) a remarkable difference is observed in its sensitiveness to light of different colours as compared with the sensitiveness of the normal eye. In the latter the spectrum appears brightest in the yellow (between the lines D and E).

The following figures represent the relative brightness of the spectrum as it appears to the 'light-adapted' eye:—

Red	(Fraunhofer line B)	32
Orange	„ „ C	94
Reddish yellow	„ „ D	640
Yellow,	D to E	1,000
Green,	E	480
Blue green,	F	170
Blue,	G	31
Violet,	H	6

In the dark-adapted eye the point of maximum brightness is shifted towards the blue end of the spectrum, so that the brightest part may lie in the green, and the red end may become quite invisible. When the light is sufficiently reduced in intensity, the whole spectrum may appear colourless. Hence, in a garden full of bright flowers, at night only differences of black and white are perceived. As morning dawns, the blue flowers and green leaves appear in their true colours, while the scarlet geraniums still appear black; while a little later with increasing illumination all the flowers are seen in their true colours. This colour-blindness to weak illumination is possessed by the extreme peripheral parts of the retina (where only rods are found) under all illuminations. This fact, combined with the fact that the sensitiveness of the dark-adapted eye to different parts of the spectrum agrees with the bleaching powers of the different parts on visual purple, suggests that we have in the retina two distinct apparatus for the appreciation of light, viz.:—

(*a*) The cones, appreciating colour differences, especially concentrated at the centre of the retina and forming the whole fovea centralis.

(*b*) The rods, sensitised by the visual purple, giving sensations only of light and darkness, and more sensitive than the cones to weak illumination. Whereas the cones are more easily excited by light in the yellow part of the spectrum, the rods are more excited by the more refrangible rays of the green and blue.

BINOCULAR VISION

Q. 1908 S L.M.

Under normal circumstances we use both eyes in seeing. Since however the visual impression produced by the two retinal images is not double but single, there must be a series of points in each retina which, stimulated simultaneously, give rise to a single impression. These points are called 'corresponding' points. Thus, when we look at a spot, the

FIG 258

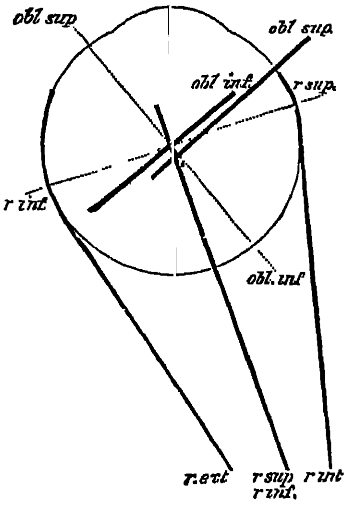


Diagram to show points of attachment and lines of action of extrinsic ocular muscles

axes of the eyes are so directed that an image of it falls on the yellow spots of the two retinæ. The images of all points to the right of this spot will fall on the nasal side of the

FIG 259

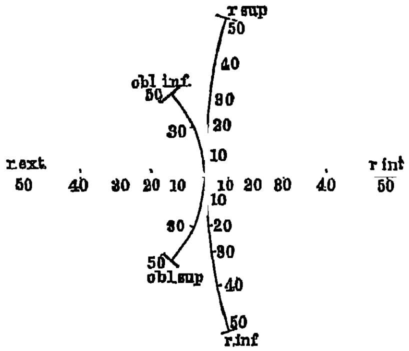


Diagram to show direction in which pupil will move under the action of the various ocular muscles right retina and on the temporal side of the left retina, and *vice versâ*. So if the right retina were cut out and placed on the left, the corresponding points in the two retinæ would be exactly over one another. In order that we may have single vision it is necessary that the images of external objects should fall on corresponding points of the two retinæ. This is effected by the harmonious co-operation of the muscles of the eyeball. These are six in number: superior, inferior, external, and internal recti, superior and inferior oblique. The action of these muscles is as follows.

Superior	rectus	moves	the centre	of the cornea	upwards and inwards
Inferior	,,	,,	,,	,,	downwards and inwards
Internal	,,	,,	,,	,,	directly inwards
External	,,	,,	,,	,,	directly outwards
Superior	oblique	,,	,,	,,	downwards and outwards
Inferior	,,	,,	,,	,,	upwards and outwards.

So the muscles required for the following movements will be—

Looking	upwards, superior recti and inferior oblique muscles
,,	downwards, inferior recti and superior oblique muscles
,,	inwards (convergence of eyes), the two internal recti
,,	to the right, the right external rectus and the left internal rectus
,,	to the left, the left external rectus and the right internal rectus

The movements of the eyes to one side or the other are spoken of as conjugate deviation. The centres of most of these movements are situated in the floor of the iter of Sylvius. The movements which involve the external recti are carried out by the nucleus of the sixth nerve, which is functionally connected with nuclei in the floor of the iter by the posterior longitudinal bundle.

If from weakness of one of the ocular muscles the optic axes cannot be made to converge to any point in the field of vision, so that the images of external objects do not fall upon corresponding points of the two retinæ, double vision results, and the patient is said to suffer from a squint. In this case the image which is formed in the sound eye is spoken of as the true, and the other the false image. From the relation in space of the false to the true image, it is possible to tell which muscle is affected.

Squi

VISUAL SENSATIONS

When a ray of light from an object to the outer side of the eye falls upon the cornea, an image of it is formed on the nasal side of the retina. If the source of light be above the visual axis, the image is formed on the lower half of the retina. Hence, whenever the retina is excited at these points, whether by light falling on the eye from without or by direct stimulation, we refer the sensation produced to some position in the outside world which the experience gained by all our other senses points out.

Thus if the right eye be turned inwards, and pressure with the finger made on the outside of the sclerotic near the outer angle of the eyelids, we have a sensation of a ring of light produced by the direct excitation of the outer part of the retina, which we refer or 'project' to a point on the extreme inner side of the eye It has often been discussed how it is that we see external objects erect when the retinal image is inverted. But we do not look at the image on the retina. The stimulation of the retina at a point on the nasal side merely gives rise to sensations which experience has taught us to recognise as coming from an object to the outer side of the visual axis.

Atrophy of the nasal half of the right retina therefore would give rise to blindness to the outer side of that eye, which would probably be recognised only when the left eye was closed.

Intensity of stimulus.—Weber's law, that the increase of stimulus necessary to cause an increase of sensation always bears the same ratio to the whole stimulus, holds good also for visual sensations.

This ratio in the case of the eye is about $\frac{1}{100}$ We can thus distinguish between two lights of 20 and $20\frac{1}{5}$ candle-power, or between two of 99 and 100 candle-power. If the illumination be excessive the law no longer holds good; and we should be unable to tell the difference between two arc lamps at a short distance, although one might be much stronger than the other, and the difference much greater than $\frac{1}{100}$ of the total light.

Duration of stimulus.—We do not know how long a stimulus of light must act on the retina in order to produce a definite sensation. But the duration is very short, since an electric spark, which is almost instantaneous in its appearance and disappearance, may excite a strong sensation of light. This momentary stimulus however, as in the case of muscle, excites a condition of activity and change in the retina which lasts a measurable period.

The sensation produced by a momentary stimulus rises sharply to a maximum and then sinks, first quickly and then more gradually. The first part of the fall, after the attainment of the maximum sensation, is more rapid in the case of strong than of weak stimuli.

This duration of the sensation after the stimulus has ceased may be so pronounced, when the stimulus is very strong, as to give rise to a definite 'after-image.' After looking at the sun for some time and then turning away, we may see an after-image that may last several seconds or minutes.

If one stimulus follows another at a very short interval we get a summation of stimuli, and the two sensations are fused into one. The interval which must intervene between two stimuli, in order that two distinct sensations may be produced, is greater when the stimuli are small than when they are intense.

This interval may be determined by causing a disc, on which alternate sectors of black and white are painted, to revolve at known rates, and noticing the time that a white sector takes to pass a given point (in the visual axis) when the sensations are just fused. If the illumination of the disc be feeble, this time will be found to be about $\frac{1}{10}$ second. If now the illumination be increased, the grey disappears, and we observe a flickering of the disc due to imperfect fusion of the separate visual sensations (cf. imperfect tetanus of muscle). In the latter case the time between two successive stimuli may be reduced to $\frac{1}{40}$ or $\frac{1}{50}$ second before apparent fusion of the sectors takes place.

The production of a circle of light when a stick with a glowing end is rapidly whirled round, and all the effects of pyrotechny, are dependent on this persistence of retinal activity after the stimulus calling it forth has ceased.

Colour Vision

If a ray of white light be passed through a prism, it is unequally refracted, so that it is widened out into a broad band or spectrum, which is variously coloured, the red rays at one end being less refrangible than the blue rays at the other. We may divide the colours of the spectrum into seven—red, orange, yellow, green, blue, indigo, violet; but the division is quite arbitrary, the colours shading so gradually into one another that no two observers would agree exactly on the limits between them. This spectrum can be recomposed by another prism in the reverse direction with the formation of white light, so that we say white light is composed of all these different colours. It might at first be thought that the retina could respond with a simple sensation to stimulation by any part of the spectrum, a low number of ether vibrations per second producing a sensation of red, a number rather higher a sensation of orange; so that the sensation produced by any part of the spectrum would be a simple colour sensation, of which there would in this case be an infinite number. But a simple analysis of our own sensations seems to show that some of the spectral colours are mixed sensations. Thus most people will say at once that orange is a mixture of red and yellow, and as a matter of fact we find that, on mixing rays from the red with others from the yellow part of the spectrum, we do get a sensation of orange. The stimulus obtained by mixing red and yellow rays is not the same as a stimulus caused by rays from the orange part of the spectrum. In the former case compound waves made up of the two wave-lengths, 656 λ and 564 λ, are falling on the retina; in the latter case a simple wave with length 608 λ; and yet the sensations produced are identical.

In order to recompose the white light it is not necessary to mix all the spectral colours. We may take a pair of colours, situated a certain distance apart in the spectrum, and by combining these form white light. Thus red with green, or blue with yellow, will give white light. Any pair of colours, which together give rise to a sensation of white, are called *complementary*. By taking three colours, such as red, green, and violet, it is possible by mixing them in various proportions to form either white light or any colour of the spectrum. The colours so formed differ from the spectral colours in being less *saturated*; *i.e.* they contain, besides the pure colour, white light.

These experiments on mixing colours can be performed in various ways

A Sectors of the different colours are painted on a disc, and the colour sensations are fused by rapid rotation of the disc (Maxwell's colour-top)

B Two small coloured discs are placed on the table, with a vertical glass plate between them It is possible so to arrange the direction of vision that the reflected image of the disc from the glass plate coincides in position with the other disc seen through the plate

C. These methods with painted discs are open to the objection that no pigments give perfectly pure colour sensations It is therefore better to use the pure colours of the spectrum itself, combining any two portions of the spectrum by means of reflectors or prisms A less perfect method is to cause light from two sources, coloured by different coloured glass, to fall on the same surface.

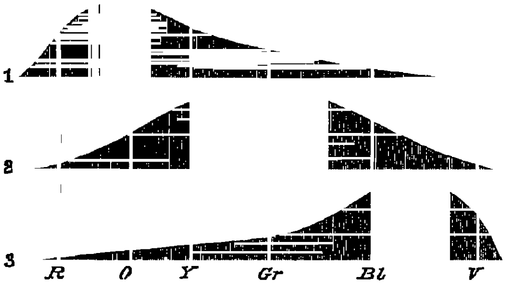
These facts show that in all probability the primitive colour sensations are few in number, and that the various colour sensations of a spectrum are not pure, but mixtures of these primary sensations. There are two theories of colour vision—the Young-Helmholtz and Hering's.

According to the former, there are three primary colour sensations—red, green, and violet—each of which is represented by a separate set of nerve-fibrils. One set of fibres is most sensitive to red rays, and only slightly sensitive to the green and blue parts of the spectrum; the second set is most sensitive to the middle, and the third set to the blue end of the spectrum. White light is produced by an equal stimulation of the three sets.

Hering distinguishes four primary colour sensations—red, yellow, green, and blue—and also considers the sensations of white and black as primary visual sensations. These sensations are placed in three groups, red and green, yellow and blue, white and black. For each pair of sensations he considers that there is a special substance in the retina, dissimilation or katabolism of which gives rise to one colour sensation; anabolism or assimilation to the other. Thus if white light falls on the retina, it causes a breaking down or katabolism of the white-black substance This breaking down excites certain fibres of the optic nerve, and produces in consciousness a sensation of white. If the light be now removed, this breaking down gives place to anabolism or building up of the white-black substance, which excites the same nerve-fibrils in a different way, giving rise to a sensation of black. The white-black substance is affected not only by white light, but also by the colours red, green, yellow, blue, and their mixtures. The other two visual substances are affected only by red and green or by yellow and blue respectively. Hence even the spectral colours do not give rise to pure sensations, there being always some mixture of a sensation of white with the proper colour sensation.

The phenomena of colour vision that we have mentioned above can be equally well explained on either theory. Thus the fact that blue and yellow together give rise to a sensation of white may be explained on the Young-Helmholtz theory by saying that the stimulation of all three sets of fibrils is equal—as will be seen by adding together the ordinates of each curve in Fig. 260 at yellow and at blue.

FIG. 260.



Curves showing sensitiveness of the three varieties of nerve-fibres to different parts of the spectrum. 1. Red fibres 2 Green fibres. 3. Violet fibres.

Adopting Hering's hypothesis, we may say that, anabolism and katabolism being equally excited in the yellow-blue substance, no change in it takes place, and the sole sensation is that produced by the stimulation of the white-black substance.

The fact that any coloured light, if very dim or if falling on only a minute part of the retina, produces a sensation of white, is more readily explicable on Hering's than on the Young-Helmholtz theory.

Cases are not rare in which a person is unable to distinguish between red and green, so that he can only tell a cherry from the leaves on the tree by its shape. Such cases may be explained on either theory. Hering's theory however seems necessary to account for the cases of complete colour-blindness which are said to occur. In these the only sensations are of light and shade, and we may suppose that the red-green and blue-yellow substances are lacking in the retina.

Contrast phenomena.—If a grey disc be placed on a piece of red paper, and the whole covered with tissue-paper, the disc will take on a greenish tinge. If the ground colour be green, the disc will appear red; if blue, the disc will appear yellow; in fine, whatever be the ground colour, the colour of the disc will be complementary to it. These effects are spoken of as simultaneous contrast.

If, after gazing steadily for some time at a red disc on a white surface, the eyes be turned towards a plain white surface, a negative after-image of the disc is seen on the paper, coloured green, *i.e.* the complementary colour of the red disc. Surrounding this the paper appears red. If we look at the sun for some time, and then turn our eyes away, there is at first a positive after-image, and we see a bright sun wherever we look. In a short time this disappears and gives way to a black sun (a negative after-image). Thus we may say that stimulation of any part of the retina with any colour is followed by a colour sensation, referred to the same part of the visual field and complementary to the first.

It has been much discussed whether these phenomena are simply effects of judgment, or whether they are produced by definite changes taking place in the retina.

Helmholtz explains them by the first hypothesis, and looks upon them as cerebral processes.

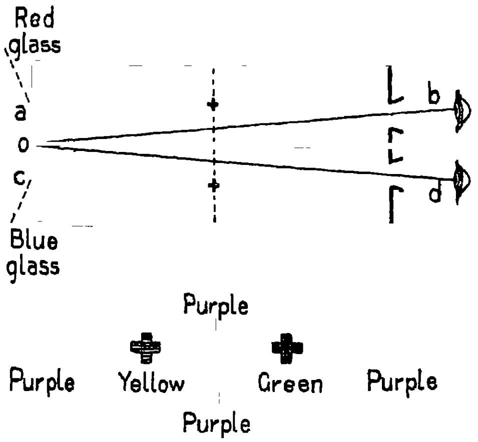
Hering, on the other hand, has extended his theory so as to embrace these phenomena, and ascribes them to definite changes in the retina, or at any rate in the peripheral part of the visual mechanism.

A corollary to his theory that we mentioned above is that, if dissimilation of a visual substance be excited at any point of the retina, assimilation of the same substance is set up in the parts of the retina immediately adjoining that point. In this way the phenomena of simultaneous contrast may be explained.

Thus if a ray of red light falls on any spot, it may be supposed to excite dissimilation of the red-green substance at this spot. This sets up assimilation of the same substance in the adjoining parts of the retina, and the red object is therefore surrounded with a green halo, which at once becomes evident if we increase our appreciation for slight colour-tones by diminishing the total amount of light by means of tissue-paper.

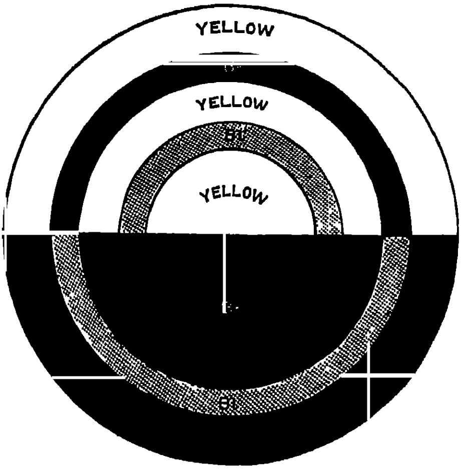
The question between the two theories is whether the contrast phenomena depend upon psychical or retinal events There is no doubt that the question must be answered in the latter sense, and that these phenomena are quite independent of the judgment of the individual. This is shown clearly by two experiments A box (Fig 261) is divided into two long compartments, *a b* and *c d* At *a* the compartment is closed by a red glass-plate and at *c* by a blue glass-plate Apertures are provided at *b* and *d* for the observer's eyes At + and + two small grey crosses are fixed about the middle of the compartment on sheets of transparent glass On looking through the openings *b* and *d* and converging the eyeballs so as to fix the line *o*, we get a fusion more or less complete of the two colours, red blue, so that the background appears purple, or there may be a struggle between the colours, at one time blue, at another red predominating To the judgment however there is one background and not two, and therefore, according to the theory of Helmholtz, the grey crosses should by contrast both acquire the same induced colour, which would be complementary for purple But it is found that the two crosses are perfectly distinct in colour, that which is seen by the eye against the blue ground

Fig 261.



yellow while that on the red ground is green, showing that the phenomena of simultaneous contrast are peripheral and not cerebral in their causation. The same fact is very definitely established by the following experiment devised by Sherrington The disc (Fig 262) presents two rings, each half blue and half black The outer ring is intensified when at rest by simultaneous contrast, the black half being seen against the surrounding yellow, while the luminosity of the blue half is increased by the effect of the surrounding black In the inner ring the blue half is darkened by contrast with the surrounding yellow while the black half is not evident at all If the disc be rotated, we get two concentric rings on an apparently homogeneous field. It is found however that the outer ring flickers long after complete fusion has taken place in the inner ring, showing that the stimulation of the retina by the outer ring is increased under the influence of contrast.

Fig 262.



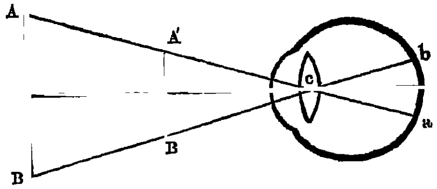
On this theory successive contrast phenomena are analogous to certain phenomena we have already studied in other tissues. If extensive breaking down of the visual stuff has been occurring, when the stimulus is removed there will be a swing back of the condition of the protoplasm of the nerve-endings in the opposite direction, and the katabolic will be replaced by anabolic changes; just as, on breaking a constant current that has been flowing through a nerve, the condition of raised irritability at the kathode gives place to a condition in which the irritability is depressed below the normal.

The improving effect on the heart of stimulation of the vagus is also exactly analogous to a successive contrast effect. During stimulation of the vagus the breaking down of the contractile substance is stopped or checked, so that building up or anabolism can go on without interruption. When the excitation of the vagus ceases there is an extra store of contractile material in the muscle-cells. This causes the beat to be more vigorous, and we may say that the increased anabolism has been followed by a period of increased katabolism, just as strong stimulation of a part of the retina with green (anabolism) gives rise to a red after-image (katabolism).

VISUAL JUDGMENTS

Size.—The apparent size of an object is determined by the magnitude of its image formed on the retina. As will be evident from the diagram (Fig. 263), the apparent size in any diameter of any given object is inversely proportional to the distance. Thus the size of the image on the retina of an object two inches long at a distance of one foot is equal to the image of an object four inches long at a distance of two feet

Fig. 263



An object can be seen if the visual angle subtended by it (the angle A c B in Fig. 263) is not less than sixty seconds This is equivalent to an image on the fovea centralis of the retina about 4 μ[1] across, which corresponds to the diameter of a cone.

Estimation of distance depends partly on muscular sensations from the degree of accommodation and of convergence of the optic axes, partly on comparisons of the apparent size of the object with that of a neighbouring object (such as a man) the real size of which is known, and partly on the amount of blurring of the outlines of the object due to the haziness of the atmosphere. The latter factor is of great importance when the object is too large and remote to be compared with others of a known size. After a storm of rain distant mountains may seem to be many miles nearer than they did before.

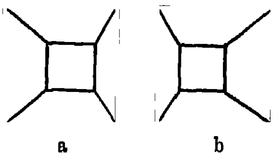
---

[1] μ = 0 001 millimetre.

Judgment of Solidity—Stereoscopic Vision

If we look at a solid object, such as a cube, with both eyes, the images formed on the corresponding points of the two retinæ are not identical, the one in the right eye representing more of the right side of the cube, and in the left eye more of the left side (Fig. 264).

FIG. 264.



If the two images (a) and (b) be so arranged that they fall on corresponding points of the two retinæ, the resulting impression is that of a solid body, in the form of a cube. This is the principle involved in the stereoscope. When only one eye is used, the external world has a much flatter appearance, although some idea of solidity is still gained from the fact that the accommodation has to be altered in order to bring different parts of the solid body into focus. The effects of light and shade also aid in the judgment of solidity.

Accessory Parts of the Eye

The eyeball is protected in front by the eyelids. These are lined internally with a delicate mucous membrane, continuous with the conjunctiva covering the anterior surface of the eyeball. This membrane is kept constantly moist by the secretion of the lachrymal gland, a small acino-tubular gland built up on the type of a serous gland, situated at the upper and outer angle of the orbit. The excess of fluid is drained off by the nasal duct, which leads from the conjunctival sac to the nasal cavity on the same side. If the eyes be kept open for some minutes, the conjunctiva covering the eyeball becomes dry, and irritation is set up. Normally the membrane, and especially that over the cornea, is kept moist and transparent by involuntary movements of the eyelids, which close or blink about twice a minute, and so distribute the lachrymal secretion over the whole conjunctival surface.

This blinking is a reflex act, the afferent channels being fibres of the fifth nerve, and the efferent the fibres of the facial nerve supplying the orbicularis palpebrarum. It is spoken of as the 'conjunctival reflex,' and is one of the last reflexes to disappear in chloroform or ether narcosis.

THE NUTRITION OF THE EYEBALL. THE INTRAOCULAR PRESSURE

The eyeball is formed of a tough inextensible capsule, the sclerotic, filled with fluid or semi-fluid contents. In order that the eyeball may be sufficiently rigid to maintain the normal relations of the various refractive media, and to afford a fixed point for the action of the ciliary muscle, this fluid must be under pressure. On connecting a small manometer with the anterior chamber, care being taken to prevent any escape of the intraocular fluid, it is found in the normal eye that this pressure is about 25 mm. Hg. On making an opening into the cornea the fluid drains away, and the eyeball becomes soft and collapsed, the cornea becoming folded, and the eye being naturally useless as an optical instrument. The fluid which flows away, and which forms the aqueous humour and also fills the interstices of the gelatinous tissue of the vitreous, contains only a minute trace of proteid, consisting in every 100 parts of 98·7 parts water and 1·2 to 1·3 total solids, of which only 0·08 to 0·12 parts consist of proteid. If a cannula be kept in the anterior chamber this fluid rapidly alters in character, becoming coagulable, and containing 3 to 4 per cent of proteids.

The intraocular fluid is continually being renewed. The eyeball receives a rich vascular supply, which forms a close network of vessels and capillaries in the choroid coat, with its prolongations the ciliary processes and iris. The chief seat of formation of the intraocular fluid is the ciliary processes.

Here there is a constant transudation of fluid from the blood-vessels into the anterior part of the vitreous cavity, the amount of the transudation varying with the pressure in the blood capillaries, being increased by any rise in the capillary blood pressure or by any fall in the intraocular pressure. Of the fluid poured out by the ciliary processes a very small proportion (perhaps one-fiftieth) passes backwards into the vitreous humour and gradually drains out of the eyeball by the lymphatic spaces of the optic nerve. By far the larger amount passes forward through the fibres of the suspensory ligament into the posterior chamber (the annular cavity between the iris in front and the lens and ciliary processes behind), and thence round the margin of the iris into the anterior chamber. From the anterior chamber it passes into the spaces of Fontana at the outer angle of the chamber, whence, *under pressure*, it can filter slowly between the endothelial cells lining the canal of Schlemm into this vessel and so into the venous system.

A considerable resistance is offered to the passage of fluid into the canal of Schlemm. Hence the constant transudation of fluid from the ciliary processes raises the intraocular pressure to 25 mm. Hg., and a continuous production of about 6 cubic millimetres of fluid per minute suffices to maintain the pressure at this height. If the anterior angle of the eye becomes blocked, the absorption of intraocular fluid becomes more and more difficult. There is therefore a rise of intraocular pressure to far above normal, and in consequence there is atrophy of the retina followed by disturbance of the nutrition of the whole eyeball. This condition of raised intraocular tension occurs in the disease known as glaucoma.

The constant renewal of the intraocular fluid is important, not only for the maintenance of the intraocular pressure, but also for the nutrition of the structures such as the lens, suspensory ligament and vitreous humour, which do not receive any vascular supply.

CHAPTER XIV

THE SPINAL CORD

SECTION 1

STRUCTURE AND TRACTS OF THE CORD

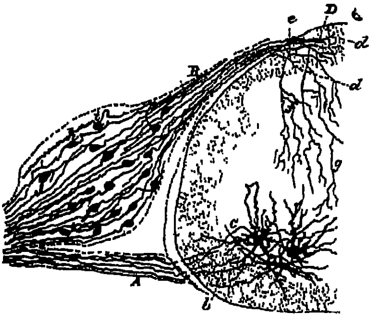
THE spinal cord and bulb may be regarded in two lights, as a centre presiding over reflex actions and as a channel of communication between the periphery and the brain. Its structure corresponds, roughly speaking, to this twofold action, consisting as it does of a tube of grey matter internally, which may be looked upon as a collection of reflex centres, surrounded externally by a layer of white matter, composed of medullated nerve-fibres and serving as simple conducting tissue. It lies in the spinal canal, protected by its three membranes, dura mater, arachnoid, and pia mater, and suspended by the attachment of its thirty-one pairs of nerves, as they pierce the dura mater The structure of the cord is best studied in cross-sections. A cross-section through the dorsal region is approximately circular, and consists of two symmetrical halves, separated in front by the anterior fissure, and behind by the posterior fissure. Each half contains a crescentic or comma-shaped area of grey matter, surrounded on its front, lateral, and mesial borders by white matter, and connected by an isthmus to the crescent of the opposite half In the centre of this isthmus is the central canal of the cord, the grey matter in front and behind it being known as the anterior and posterior grey commissures. At the base of the anterior fissure the white matter is continuous between the two halves of the cord, forming the anterior white commissure.

The Nerve-roots

Each nerve of the thirty-one pairs that arise from the spinal cord has two roots, anterior and posterior. The anterior root arises by several bundles from the antero-lateral part of the cord; the posterior root arises as a single bundle, emerging from the spinal cord opposite the posterior horn of grey matter. The two roots join to form the trunk of the spinal nerve. On the posterior root, just before it joins the anterior root, is situated a ganglion, the posterior root ganglion.

If we study the development of these roots, we find that they have different origins. Whereas the axis-cylinders of the anterior roots are formed by the outgrowth of the axons of cells in the grey matter of the cord, chiefly in the anterior cornu (Fig. 265), the posterior roots are derived from a separate mass of cells formed from the epiblast close to the dorsal surface of the cord. These epiblastic cells become oval and send out a process at each extremity, one process growing into the spinal cord, while the other meets the anterior roots and grows with these downwards towards the periphery. In some animals, such as fishes, the cells of the posterior root-ganglia retain this bipolar character throughout life, and this is also the case with the analogous ganglion situated on the course of the auditory nerve in the cochlea, the so-called spiral ganglion. In all higher vertebrates the two processes of the cells of the spinal ganglia become approximated in the course of growth and finally

FIG 265



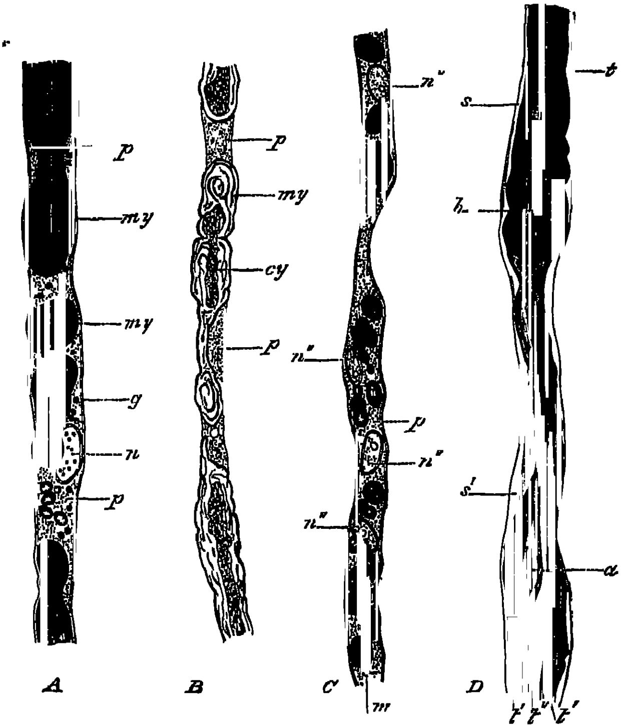
Transverse section of spinal cord of chick to show developing nerve-roots (stained by Golgi's method) (Ramón y Cajal) A, anterior root-fibres growing from the anterior cornual cells, c, B, posterior root-fibres passing from bipolar cells of ganglion into cord arise from the cell as one process which divides into two by a T-shaped junction at the first node of Ranvier.

Thus from the point of view of development, the nerve-fibres making up a mixed spinal nerve are of twofold origin, and represent the arms or elongated processes of two distinct sets of cells. If a unicellular animal be cut into two parts, it is found that the half containing the nucleus will regenerate the missing part and will continue to live, whereas the part which contains no nucleus, although able for a short time to carry out movements or even to ingest food-granules, is unable to assimilate its food and grow, and finally dies. Exactly the same thing happens in the case of a nerve-cell. If we cut through that part of the cell which forms the axis-cylinder of a nerve-fibre, the part cut away, although for a time excitable and able to conduct impulses, finally dies; whereas the part attached to the cell-body with its nucleus continues to live and may under favourable circumstances regenerate the part that has been cut off. These facts furnish the basis of a method for determining the exact situation of the nerve-cell from which a given axis-cylinder is derived.

We have already seen that section of a peripheral nerve causes, after a small initial rise, a gradual fall of irritability in the part of the nerve below the section. This goes on to complete loss of irritability, and on microscopic investigation it is found that the physiological change is accompanied by definite progressive structural changes.

About four days after the section (in mammals) the myelin forming the medullary sheath of the nerve-fibres in the peripheral part of the nerve becomes segmented, and breaks up into drops of various size (Fig. 266). A little later the axis-cylinder is also broken across, so that there is no longer any physiological continuity in the nerve-fibre This is followed by enlargement and proliferation of the internodal nuclei; the protoplasm within the primitive sheath increases in quantity, and the drops of myelin are gradually absorbed and disappear. Finally, about the twenty-first day or later, the original structure of the nerve-fibres has entirely disappeared, and they consist merely of a tubular sheath, containing nuclei and structureless protoplasm. If no regeneration can take place these structures also disappear, giving place to simple connective tissue. If however, after the section, the two ends of the nerve have been kept in close apposition by means of sutures, regeneration of the peripheral part of the

FIG 266.



Degeneration and regeneration of nerve-fibres in the rabbit (Schafer, after Ranvier) A, part of a nerve-fibre in which degeneration has commenced in consequence of the section, fifty hours previously, of the trunk of the nerve higher up; *my*, medullary sheath becoming broken up into drops of myelin, *p*, granular protoplasmic substance which is replacing the myelin, *n*, nucleus, *g*, neurilemma B, another fibre in which degeneration is proceeding, the nerve having been cut four days previously, *p*, as before, *cy*, axis-cylinder partly broken up, and the pieces inclosed in portions of myelin C, more advanced stage of degeneration, the medullary sheath having almost disappeared, and being replaced by protoplasm in which, besides drops of myelin, are numerous nuclei which have resulted from the division of the single nucleus of the internode. D, commencing regeneration of a nerve-fibre Several small fibres, t' t'', have sprouted from the somewhat bulbous cut end, *b*, of the original fibre, *t*; *a*, an axis-cylinder which has not yet acquired its medullary sheath; *s*, *s'*, primitive sheath of the original fibre A, C, and D are from osmic preparations, B from an alcohol and carmine preparation nerve takes place. New axis-cylinders grow out from the old axis-cylinders of the central part of the nerve at the node of Ranvier just above the point of division, and these grow down into the structureless protoplasm filling the sheaths of the peripheral nerve-fibres, thus restoring functional continuity The myelin sheaths of the regenerated nerve-fibres make their appearance rather later. Nerve-fibres have already been spoken of as being enormously elongated cell-processes, and it seems that a fibre degenerates whenever it is separated from the cell of which it is an outgrowth, and must be regenerated by a renewed outgrowth from this cell. We may look upon the nerve-cells as presiding over the nutrition of the fibres which spring from them; and they are therefore called the 'trophic centres' of these fibres. If a nerve be divided, only that half which is separated from its trophic centre will degenerate. This fact was first pointed out clearly by Waller, and hence the method of diagnosing the course of tracts in the central nervous system is named the Wallerian method.

A large majority of the white fibres of the spinal cord are dependent for their nutrition upon their continuity with a nerve-cell, and if this be abolished the part of the nerve-fibre severed from the cell degenerates. If the anterior root be divided, the part attached to the cord remains intact, but the whole peripheral part of the fibres degenerates, so that in a section of the mixed nerve the degenerated motor-fibres can be identified (Fig. 267, II).

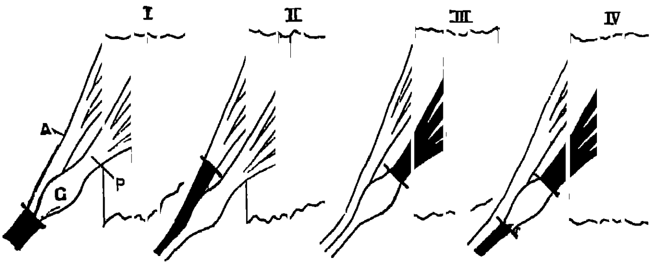
If the posterior root be divided between the ganglion and its junction with the anterior root, all the sensory fibres in the mixed nerve below the junction degenerate. If however it be divided between the ganglion and the cord, the sensory fibres in the mixed nerve remain intact, but the central parts of the fibres degenerate right up into the cord, and may be traced in the cord as far up as the medulla.

It has already been stated that the anterior root is motor or efferent, and the posterior root sensory or afferent. The evidence for this is as follows:—If the anterior root be divided, the muscles supplied by the nerve are paralysed. Excitation of the peripheral end of the anterior root will cause them to contract. Excitation of its central end has no effect.

Section of the posterior root causes loss of sensation in its area of distribution. Stimulation of its peripheral end has no effect. Stimulation of its central end causes marked signs of pain, such as struggling, crying out or, in a curarised animal, rise of blood-pressure.

In some cases we may find that stimulation of the peripheral end of the anterior root gives rise to evidence of pain. This is spoken of as *recurrent sensibility*, and is due to stimulation of fibres which leave the cord by the posterior roots, and after travelling some distance towards the periphery turn back and run up in the anterior root. Recurrent sensibility is abolished, as would be expected, by division of the posterior root.

FIG. 267.

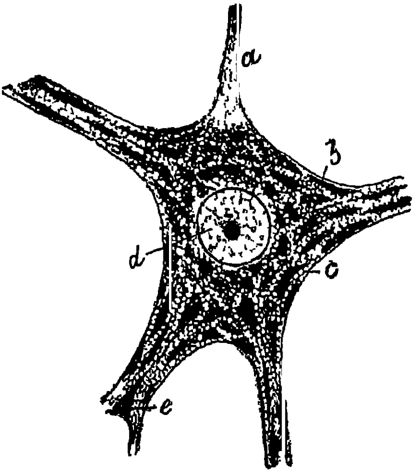


Figures (from Yeo) to illustrate the degree and direction of degeneration as a result of section of the spinal roots I, division of whole nerve below ganglion II, division of anterior root III, division of posterior root above ganglion IV, division of posterior root above and below ganglion.

The Grey Matter of the Cord

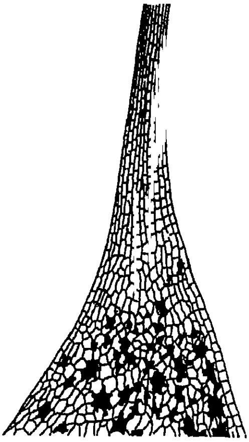
The crescentic mass of grey matter in each half of a cross-section of a cord is larger in front than behind, the anterior and posterior halves being spoken of as the anterior and posterior horns or cornua respectively (Fig. 272, p. 593). Each horn is again divided into the caput or head, forming the large extremity, and the neck, which is the narrower part by which the caput is connected with the central mass of grey matter. When examined in section, the grey matter at first presents an inextricable confusion of nerve cells and fibres of all descriptions. But of late years various methods have come to our assistance in the unravelling of the tangled mass. The most important of these methods are the methylene blue method of Ehrlich and Golgi's silver chromate method with its various modifications. Both these methods stain nerve-cells with all their processes, and since in a given segment of the cord only a few of the nerve-cells are stained, it is possible to trace their processes through a considerable thickness of the cord. The grey matter consists of nerve-cells with their processes, of the branching terminations of various nerve-fibres derived from the white matter of the cord or the posterior nerve-roots, and of the supporting framework or neuroglia All the nerve-cells of the cord are multipolar (Fig. 268). The processes however are of two kinds. One kind of process, the neuraxon or *axon*, of which only one is present, is in most cases prolonged into a nerve-fibre, of which it becomes the axis-cylinder, generally acquiring at the same time a medullary sheath. This process may send off a few fine branches, the so-called *collaterals*, but in most cases does not undergo any extensive branching until nearing its periphery, where it may break up into the rich arborisations with which we are already acquainted as the

FIG. 268.



Nerve-cell from the spinal cord, stained by Nissl's method. *a*, axis-cylinder process or axon, *b*, protoplasm of cell, consisting of *c*, fibrillated ground substance, and *e*, the granules of Nissl, *d*, nucleus (Lenhossek) motor and sensory nerve-endings. All the other processes of the cell are generally thicker at their origin than the axon, and very rapidly break up into branches which end freely in the neighbouring grey matter. In many cases these *dendrites* have serrated margins—an appearance especially well-marked in certain cells of the cerebrum and cerebellum. The body of the cell, sometimes called the perikaryon, is granular and surrounds a large vesicular nucleus with well-marked nuclear membrane, which only stains faintly with nuclear dyes. By special methods a fibrillation of the protoplasm has been demonstrated, the fibrillæ sweeping across the cell from process to process, and many converging towards the point of origin of the axon (Fig. 269). While some observers regard this fibrillation as an artefact due to the coagulating reagents employed, others attach extreme importance to it, and look upon the fibrillæ as the essential conducting elements of the central nervous system, continuous from cell to cell and throughout the whole body.

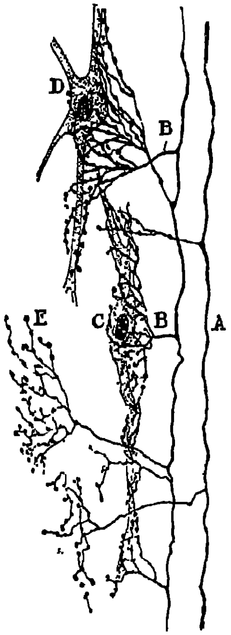
FIG 269.



The point of origin of the axon, the 'nerve-hillock,' highly magnified, to show absence of Nissl's granules from the origin of the process. (Held)

According to most observers however, such an anatomical continuity does not exist, at any rate in vertebrate animals. All the constituents of the central nervous system arise from cell-units, and so far as we can tell, the processes of these cells do not grow together but simply remain in contact. Thus the axis-cylinder of an anterior cornual cell ends on a muscle-fibre as an arborisation, the branches of which end freely on the surface of the fibre. The cells of the central nervous system are influenced in the same way. An axon from the periphery or from another part of the central nervous system ends in an arborisation in contact either with the cell-body or with the dendritic processes (Fig. 270). Any impulse arriving

FIG 270

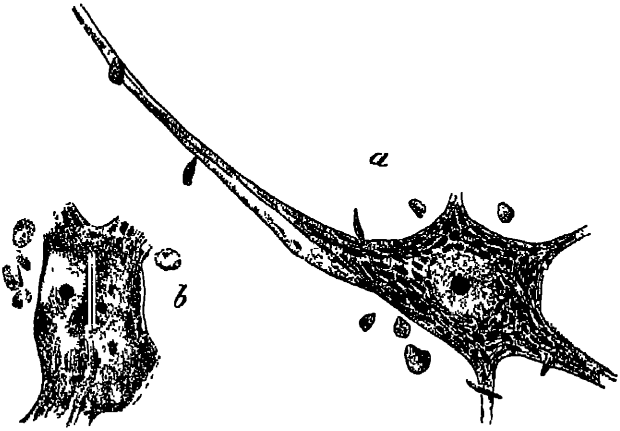


Arborisation of collaterals from the posterior root-fibres round the cells of the posterior horn (Ramón y Cajal)

at this arborisation sets up a new impulse in the cell-body, just as a motor impulse descending a nerve sets up a new excitatory impulse in the muscle with an energy considerably in excess of the original nerve-impulse. Thus the whole nervous system can be regarded as made up of a numberless array of nerve-cells with their processes (*neurons*), the activity of each being regulated by the connections of its dendrites and the destiny of its axon. It is possible that the office of each cell is not merely to transmit the disturbance arriving at it, but to send it on with increased energy, acting like a battery relay in a telegraphic circuit. In all cases where there is a distinction between the dendrites and the axon, the direction of conduction seems to be in the dendrites towards the cell, cellulipetal, and in the axon away from the cell, cellulifugal. In bipolar cells, as in the spinal ganglia, it is impossible as a rule to draw any distinction between the two processes

If the nerve-cells serve as relays of energy, nervous activity must be associated with a using up of material in the cell; and many attempts have been made to discover histological evidences of nerve-cell activity. Of importance in this connection is the presence in the nerve-cells of certain bodies which are known as Nissl's granules. If a section of nervous tissue fixed with alcohol, formol, or corrosive sublimate be stained with basic dyes such as methylene blue or toluidin blue, the bodies of the cells are seen to contain a number of coarse angular granules or masses arranged more or less symmetrically round the cell, and extending for a considerable distance along the dendrites (Fig. 271, *a*). The axon and that part of the cell from which it arises (the nerve-hillock) are quite free from these granules (cf. Fig. 269). As the result of stimulation, changes have been described both in these granules

FIG 271.



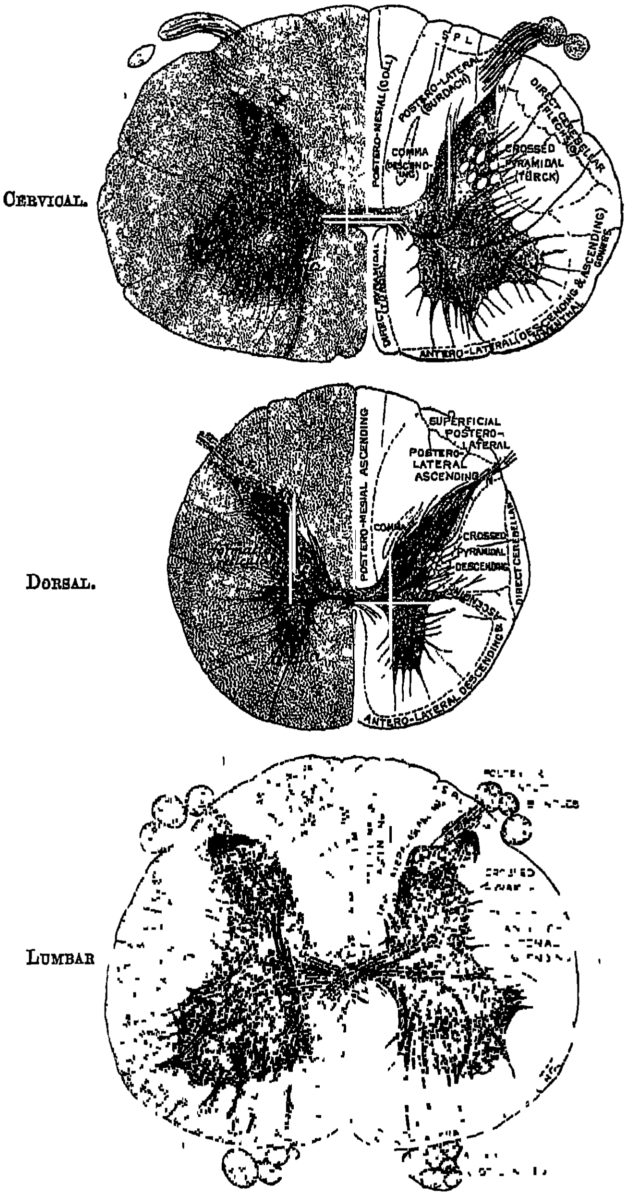
Cells from the oculomotor nuclei thirteen days after section of the nerve on one side *a*, cell from healthy side; *b*, cell from side on which nerve was divided (Flatau).

and in the nucleus of the cell. Of more practical importance however are the changes produced in these granules by section of the axon itself. As a matter of fact, although division of an axon causes the more profound changes in that part which is separated from the cell-body or *perikaryon*, the temporary or permanent loss of function does not leave the cell unaffected. It was long ago shown that amputation of a limb was followed after many years by a shrinkage and atrophy of all that portion of the grey matter from which the nerves to the limb were derived. The introduction of Nissl's method has shown that an appreciable change is produced within a few weeks, the granules losing their individuality and becoming broken up, so that the whole cell takes on a diffuse blue stain (Fig. 271, *b*). This change is followed after some considerable time by a gradual atrophy of the cell and all its processes. It is sometimes spoken of as secondary, or better as 'retrograde' degeneration.

The grey matter is thus made up of nerve-cells embedded in a close felt-work of fibres of various descriptions, fine medullated nerve-fibres coming in as collaterals from the surrounding white matter and breaking up into naked arborisations. Branching axis-cylinders, which begin and end in the grey matter itself, as well as the richly branched dendrites of the various nerve-cells, all these elements are embedded in and supported by the special connective tissue of the nervous system, the neuroglia.

The neuroglia resembles the rest of the nervous system in being of epiblastic origin. The cells forming the primitive neural groove are of two kinds, the neuroblasts, from which the nerve-cells are derived, and the spongioblasts. These latter at first form a continuous lining of the central canal, and send out one process to the periphery of the cord. This process branches freely, and in course of time some of the cells wander out into the substance of the cord and acquire many processes, which run out in all directions and cross those of adjacent cells. In the adult cord the cell-bodies of these neuroglia cells either disappear altogether or are reduced to little more than the nucleus, so that the neuroglia consists of a rich felt-work of branching fibres crossing each other in all directions and forming a framework for the nervous elements of the cord.

FIG 272.


CERVICAL.
S P L
POSTERO-MESIAL (GOLL)
POSTERO-LATERAL (BURDACH)
COMMA (DESCENDING)
DIRECT CEREBELLAR (FLECHSIG)
CROSSED PYRAMIDAL (TÜRCK)
DIRECT PYRAMIDAL
ANTERO-LATERAL (DESCENDING & ASCENDING) (VENTRAL) (GOWERS)
DORSAL.
POSTERO-MESIAL ASCENDING
SUPERFICIAL POSTERO-LATERAL
POSTERO-LATERAL ASCENDING
COMMA
CROSSED PYRAMIDAL DESCENDING
DIRECT CEREBELLAR
ANTERO-LATERAL DESCENDING & ASCENDING
LUMBAR

Sections of human spinal cord from the lower cervical, mid-dorsal, and mid-lumbar regions, showing the principal groups of nerve-cells, and on the right side of each section the conducting tracts as they occur in the several regions (magnified about 7 diameters). (E A Schafer) *a*, *b*, *c*, groups of cells of the anterior horn, *d*, cells of the lateral horn, *e*, middle group of cells, *f*, cells of Clarke's column, *g*, cells of posterior horn, *c c*, central canal, *a c*, anterior commissure.

In accordance with its epiblastic origin, the neuroglia presents no chemical resemblances to the group of connective tissues Its main constituent is a body allied to keratin, known as neuro-keratin, giving all the reactions of proteins, but distinguished from the ordinary members of this group by its insolubility in the digestive juices as well as by the high proportion of sulphur in its molecule

This neuroglia, though extending through the whole cord, is especially concentrated at two points, viz. in the immediate vicinity of the central canal and at the head of the posterior horn, where mingled with small nerve-cells it forms a sort of cap to the grey matter and is known as the substantia gelatinosa of Rolando.

The grey matter of the cord may be considered as a continuous tube formed by the fusion of a series of paired ganglia, each of which innervated one body segment. This regular arrangement has been modified by the development at a later period of the limbs, and the necessary growth of new cells to supply the limbs. Hence we find a considerable enlargement of the grey matter in two situations, the cervical enlargement corresponding to the brachial plexus, and the lumbo-sacral enlargement which gives origin to the nerves of the hind limb

The cells of the grey matter are arranged in definite groups or columns, some of which extend throughout the whole length of the cord, whilst others are confined to certain regions. These columns are—

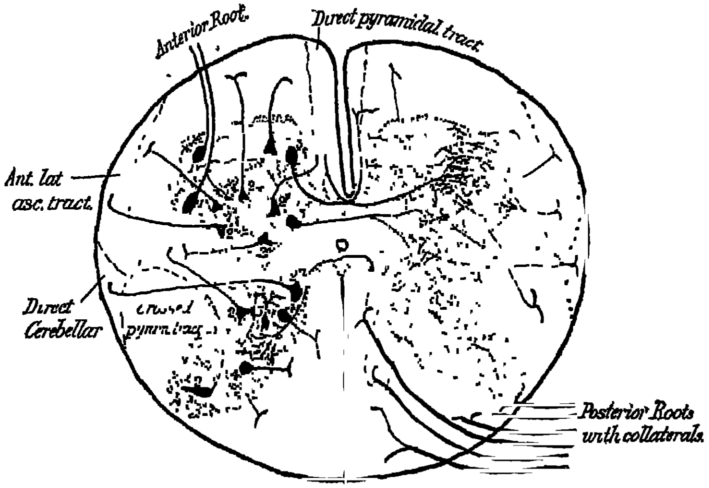
1. In the anterior cornu, two sets of cells, the anterior or median and the external groups. These cells are the largest in the cord; they have many processes, one process being continued into the medullated nerve-fibre of an anterior root, the other processes (dendrites) breaking up into a fine meshwork of non-medullated fibrils, which become lost in the meshwork of the grey matter. The external group (*b*, Fig. 272) is especially connected with the motor nerves to the limb muscles.

2. The lateral column or intermedio-lateral tract, chiefly marked in the dorsal and upper part of the lumbar spinal cord. These cells are almost certainly connected with the visceral outflow which occurs in this region. Their axons pass out by the anterior roots, and then by the white rami communicantes to the sympathetic system, in some ganglion of which they terminate.

3. The cells of the posterior horn, small multipolar cells.

4 Clarke's column or posterior vesicular column (Fig. 272, *f*), reaching from the seventh or eighth cervical nerve to the third lumbar nerve, and represented opposite the second and third cervical nerves by a small group of cells and possibly also in the sacral region by a group known as Stilling's nucleus. The cells composing this column are large and fusiform, with their long axes parallel to that of the cord, so that in cross-section they have the appearance of small round cells.

Fig 273



Spinal cord (after Lenhossek)

On left side of figure are shown the nerve-cells with their axis-cylinder processes On the right side the distribution of the chief collaterals. 1 Motor cells 2 Cells of the columns 2*a* Cells of Clarke's column, sending processes across into direct cerebellar tract. 3, 4, and 5. Commissural cells.

A more general classification of the nerve-cells may be based on the destination of their nerve-fibre processes (Fig. 273). In this way we may distinguish—

(1) Motor cells. These are the large cells already described in the anterior cornua. Their axis-cylinder processes all run out into an anterior nerve-root, and end for the most part in the motor end-plate on a muscular fibre.

(2) Cells of the columns. The nerve-processes of these run out into the white matter, and the majority ascend in one of the columns of the cord. We find these cells in the anterior and lateral cornua, sending fibres into the anterior and lateral columns. There are also a few in the

posterior cornua which send their processes into the posterior columns. The best-marked group however is that already described as forming Clarke's column. These send their nerve-fibre processes right across the grey matter into the lateral column of the same side, where they turn upwards, forming a distinct tract of fibres—the direct or posterior cerebellar tract.

(3) Commissural cells. This class embraces a number of cells of different sizes and shapes. Their axons either end in the grey matter of the same side, or traverse the cord to form connections with the grey matter of the other side. Many of these fibres pass through the anterior white commissure. Among these we find the Golgi type of cell, *i.e.* a cell whose axon begins to divide almost immediately after leaving the cell, and branching profusely ends in the near neighbourhood of the cell from which it started.

The White Matter of the Cord

The white matter consists almost exclusively of medullated nerve-fibres, which run for the most part longitudinally. They are of various sizes, some of the smaller fibres being branches (collaterals), which have been given off from the larger ones, and which will shortly turn into the grey matter. In section they resemble closely the fibres of an ordinary peripheral nerve, but they differ from these in that they have no primitive sheath or neurilemma. Each consists simply of an axis-cylinder surrounded by a thick medullary sheath, the whole embedded in a tube formed by the neuroglia The white matter is divided by the anterior and posterior fissures, and the nerve-roots into anterior or ventral, lateral, and posterior or dorsal columns. A further subdivision of the anterior column into antero-median and antero-lateral, and of the posterior column into postero-median and postero-lateral, is indicated by slight grooves on the surface of the cord in the cervical region. In order however to arrive at a knowledge of the origin, course, and destiny of the fibres composing the white matter, we must have recourse to indirect methods. The following methods may be employed :

1. Wallerian method. If the cord be cut across transversely, some tracts of white matter will degenerate in the cord above the lesion (ascending degeneration), while other tracts will degenerate in the cord below the lesion (descending degeneration), according as the cells of origin of the fibres

lie below or above the lesion. In this way the white matter may be divided into ascending and descending tracts.[1] This method may be applied in two ways. The spinal cord may be cut and the animal kept alive for three to six months. At the end of this time all the degenerated fibres have disappeared and their place is taken by neuroglia. On staining sections with carmine, the degenerated part therefore looks pinker than the rest of the section. A better method is to treat the sections by some process such as Weigert's, which stains the normal medullary sheaths black. By this treatment, the degenerated area is at once detected by its failure to take the stain.

This method will not serve to display the presence of isolated degenerated fibres among a mass of normal fibres. For this purpose we may use Marchi's method, which is based on the fact that the medullary sheath, when it breaks up, undergoes chemical change, and acquires the composition of ordinary neutral fat. If a tissue be placed in Muller's fluid for a fortnight, and then in a mixture of osmic acid and Muller's fluid, no blackening of the normal medullary sheath is produced, although fat is blackened by the osmic acid in the ordinary way. The presence therefore of one or two degenerated fibres in a section of spinal cord will be at once evinced by the appearance of black dots in the otherwise unstained section. In employing this method, the cord must be hardened before the broken-up medullary sheath has begun to be absorbed, *i.e.* about two or three weeks after the lesion.

2. Method of retrograde degeneration. This is based on the changes undergone by Nissl's granules (chromatolysis) as the result of section of the axon of a cell. For example, the hypoglossal nerve may be divided and three weeks later the animal killed and sections of the medulla cut and stained by Nissl's method. The distribution of the cells of origin of this nerve is at once shown by the marked changes in the cells on the side of the lesion as contrasted with the normal cells on the opposite side (cf Fig. 271, p. 591).

3. Developmental method (Flechsig). This method is

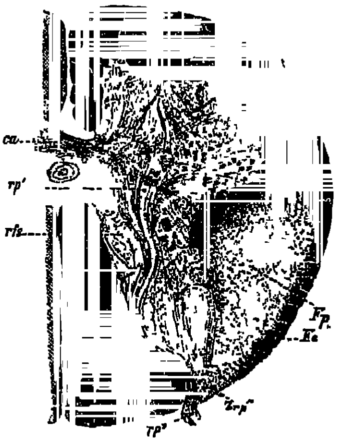
---

[1] A caution is here necessary It is often assumed that a tract which degenerates upwards is necessarily afferent in function, and *vice versâ* But the result of section of a peripheral nerve, after which sensory as well as motor fibres degenerate below the section, shows that the direction of degeneration is not necessarily the same as the direction of conduction

founded on the fact that, when the nerve-fibres are first formed in the fœtal cord, they are non-medullated, and the different tracts of the cord acquire a medullary sheath at different intervals, the pyramidal tracts being latest of all in acquiring their sheath (Fig. 274).

4. Electrical method. The passage of a nerve-impulse along the cord, as along a nerve, is accompanied by an electrical change (current of action). It is possible to find out by what path the electrical change travels, and thereby to determine the path of the impulse of which the electrical change is the concomitant (Gotch and Horsley).

FIG 274



Section through the cervical spinal cord of a new-born child, stained by Weigert's method, to show absence of medullation in pyramidal tract *ca*, anterior commissure, *Fp*, crossed pyramidal tract, *Fe*, direct cerebellar tract, *Zrp*, posterior root zone, *rp'*, posterior root-fibres (Bechterew)

5. Experimental method. Different parts of the white columns may be cut through, and the effects observed that are produced in this way on the conduction of motor or sensory impulses. Evidence in this direction is also furnished by the clinical results of lesions of various parts of the cord.

By a combination of these methods the following conclusions have been arrived at. The white matter of the cord may be divided into ascending and descending tracts (Fig. 275; see also Fig. 272).

A. *Descending tracts.*—If the spinal cord be divided in the cervical region, degeneration of two distinct tracts in the anterior and postero-lateral columns is produced. These are the anterior or direct and the crossed pyramidal tracts. The fibres composing these tracts are derived from the pyramidal cells in the motor area of the cerebral cortex, and are therefore found degenerated if the motor area of the cortex is destroyed The crossed pyramidal tracts are derived from the other side of the cerebral cortex and have crossed the middle line at the lower part of the medulla, at the pyramidal decussation. The anterior tracts continue the course of the pyramids in the medulla for a time, but cross gradually by the anterior commissure on their way down the cord. Finally, therefore, all the fibres reach the crossed pyramidal tracts. They end in the spinal cord by turning into the grey matter, where they break up into a fine bunch of fibrils in close connection with the motor cells of the anterior cornua (or, according to Schafer, with the cells of the posterior cornua). On their way down the cord they give off fine side branches or 'collaterals,' which run into the anterior cornu and there terminate, thus establishing connections between one cortical cell and the anterior cornual cells of several different segments of the spinal cord. It is therefore concluded that they carry motor impulses from the cerebral cortex to the ganglion cells of the cord. Destruction of these columns by disease or otherwise causes the abolition of voluntary control over the muscles.

FIG. 275

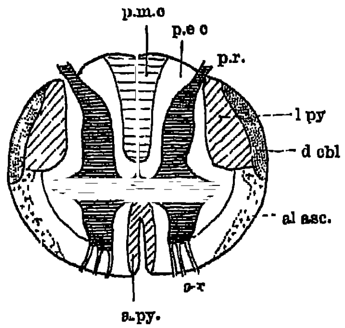


Diagram of spinal cord. a r Anterior spinal nerve-roots p r Posterior root a py Anterior pyramidal tract l py Lateral pyramidal tract d cbl Direct cerebellar tract p m c Posterior median column p e c. Posterior external column al asc. Antero-lateral ascending tract

Ventrally to the pyramidal tracts there is a fairly compact group of fibres which degenerate downwards This is known as the pre-pyramidal or rubro-spinal tract, since its fibres can be traced up to the cells in the red nucleus, a mass of grey matter in the mid-brain situated ventrally to the nucleus of the third nerve.

There are also some scattered fibres in the antero-lateral column, which degenerate in the downward direction. These were formerly supposed to be derived from the cerebellum of the same side, but it has been shown that they are in all probability derived from Deiters' nucleus in the medulla, which stands as a downward transmitting station between cerebellum and cord. These are sometimes known as the vestibulo-spinal tract.

Fig 276

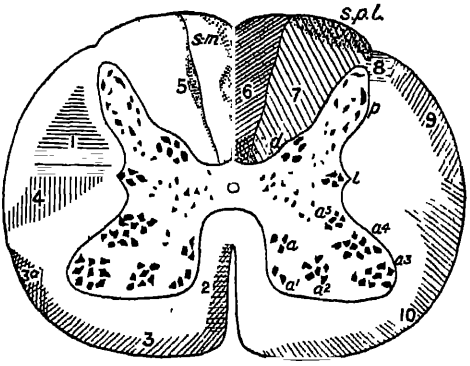


Diagram (from Schafer) showing the ascending (right side) and the descending (left side) tracts in the spinal cord.
1 Crossed pyramidal 2 Direct pyramidal 3 Antero-lateral descending. 3*a* Spino-olivary descending (bundle of Helweg) 4. Pre-pyramidal (rubrospinal) 5 Comma 6 Postero-mesial 7. Postero-lateral 8 Lissauer's tract. 9 Dorsal (ascending) cerebellar 10 Antero-lateral ascending *s m* Septo-marginal *s p l.* Dorsal root zone *a.* Anterior horn cells *i* Intermedio-lateral horn *p* Cells of posterior horn. *d* Clarke's column. The fine dots represent the situation of the 'internuncial' or 'endogenous' fibres of the spinal cord

Beside these tracts there is a little collection of fibres in the posterior columns which degenerates for a few segments of the cord *below* a transverse lesion (the 'comma' tract). They consist largely of fibres derived from the posterior roots, which divide into ascending and descending branches as they enter the cord, but also contain probably certain fibres derived from cells in the cord and serving to connect one segment of the cord with another.

FIG 277.

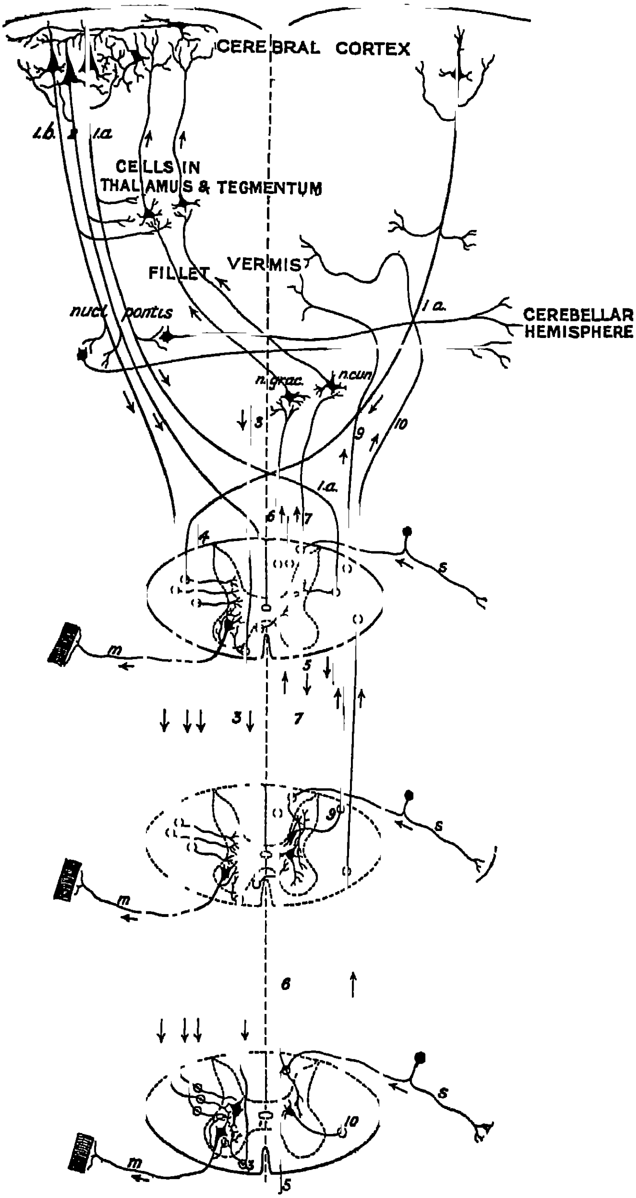


Diagram showing the course, origin, and termination of the principal tracts of the spinal cord (Schafer)

'*Descending tracts*'—1*a* A fibre of the crossed pyramidal tract 1*b*. An uncrossed fibre of the pyramidal tract passing to the lateral column of the same side 2 A fibre of the direct pyramidal tract 3. Antero-lateral descending tract 4 Pre-pyramidal tract 5. Comma tract '*Ascending tracts.*'—6 Postero-mesial 7. Postero-lateral tract 9 Dorsal cerebellar. 10 Antero-lateral ascending. *m*. Motor nerve fibre. *s* Sensory roots

B. *Ascending tracts.*—The tracts which degenerate in the cord above a transverse section are four in number:

1. The postero-median, as far up as the nucleus gracilis in the medulla.

2. The posterior root-zone for one or two segments above the lesion.

3. The direct or posterior cerebellar tract as far as the cerebellum.

4. The antero-lateral ascending tract or anterior cerebellar tract. The fibres of this tract also end in the cerebellum near those of No. 3, but take a more circuitous path than those of the latter tract.

Division of all the posterior roots on one side causes degeneration of the posterior root-zone and postero-median column on the same side, as well as of some fibres in the 'comma' tract. Hence the fibres of these columns have their trophic centres on the ganglia of the posterior roots. The other two ascending tracts do not degenerate after section of the posterior roots, and must therefore have their trophic centres in the cells of the grey matter of the cord. We have already mentioned that the direct cerebellar tract is derived from the cells of the posterior vesicular column of Clarke, and it has been stated that the antero-lateral ascending tract also originates in the same way. All these tracts, on their way up the cord, send off branches or collaterals which terminate round the cells of the grey matter in the different segments of the cord. Some of these run from the posterior root-fibres directly across to the anterior cornu of the same side, and thus subserve the simplest forms of reflex action (cf. Figs. 273 and 276).

The deeper parts of the white matter, near the grey matter, in the anterior and lateral columns, are known as the ventral and lateral basis bundles. They contain fibres, some ascending, some descending, which seem to connect different levels of the cord, some fibres of which can be traced from the cervical to the lumbo-sacral region. Besides these 'internuncial' fibres, there is a large number of fibres in the white matter which do not degenerate more than one spinal segment either above or below a transverse section of the cord. These are supposed to be commissural, serving to connect one segment of the cord with the other.

Section 2

PATHS OF IMPULSES IN THE CORD

All impulses which pass through the cord form parts of reflex actions, carried out either by the cord alone, or with the intervention of the higher parts of the central nervous system, the bulb, cerebellum, or cerebral hemispheres. We may therefore conveniently distinguish the local spinal reflexes from the brain reflexes, including the complex ones involving conscious sensation and volition. All these reflexes are inaugurated by afferent impulses, which reach the central nervous system along sensory nerve-roots.

The posterior spinal (sensory) roots at their entrance into the cord divide into two bundles. The smaller of the two, situated more laterally and consisting of fine fibres, enters opposite the tip of the posterior horn and turns up at once in Lissauer's tract, a bundle of fine longitudinal fibres lying close to the periphery of the cord. The fibres seem to pass into and end in the substance of Rolando. The larger median bundle of coarse fibres passes into the postero-external column. Here each fibre divides into a descending and an ascending branch, the former running in the comma tract, the latter in the posterior columns up as far as the gracile and cuneate nuclei of the medulla. Both of these branches give off collaterals in the whole of their course, most numerous near the point of entry of the nerve. These collaterals may be divided into four sets according to their destination.

1. Fibres ending round cells of anterior horn on same side or crossing by posterior commissure to grey matter on other side.
2. Fibres ending in grey matter of posterior horns.
3. Fibres ending round cells of Clarke's column.
4. Fibres to lateral horn.

Since the motor nerves arise from the anterior horn cells, the first set, the so-called sensori-motor collaterals, represent the shortest possible spinal reflex path. The second group may also represent a spinal reflex path with two relays of cells, and therefore greater choice of response and longer reaction time.

The third set puts into action the cerebellar tracts which arise from the cells of Clarke's column, and therefore call into play a much more complicated mechanism, the limits of whose action it would be difficult to define. The collaterals to the lateral horn probably represent the afferent tracts of the various visceral and vaso-motor reflexes which we studied in the earlier chapters.

In dealing with the reflexes involving the co-operation of the brain we find no special tracts devoted to those impulses which affect consciousness as sensations. All tracts going towards the cerebral hemispheres are interrupted by cell relays in the medulla or cerebellum, and must serve as afferent channels for unconscious as well as for conscious reactions. The quality of an afferent impulse can only be defined by its origin, or by its effect on consciousness ; and much discussion has arisen as to the exact path of the various cutaneous and muscular sensations in the cord.

It is evident that an impulse may travel to the cortex by way of the two cerebellar tracts through the cerebellum, or by way of the posterior columns through the intermediation of the bulbar nuclei, or by a series of relays from one segment of the cord to another through grey and white matter alternately.

It is supposed that all of the ascending tracts may convey afferent impulses from the posterior roots to the brain, although evidence as to the part taken by each tract is very conflicting. The following account represents the views which may be regarded as the most probable (Page May): Pain impulses, on entering the cord by the posterior roots, cross to the other side at once, and then pass up, chiefly in the antero-lateral ascending tract of Gowers, as far as the optic thalamus. Sensations of heat and cold take a very similar course. Hence they are generally affected by lesions of the cord in the same way as pain sensations. Impulses of touch and pressure, after entering the cord, pass up in the posterior column of the same side for four or five segments, then cross gradually and pass up in the opposite anterior column. Muscular sensibility, including the impulses from joints and tendons, take two courses. Those which do not reach consciousness, and are involved in the involuntary guidance of muscular movements, run up chiefly in the anterior and posterior cerebellar tracts of the same side. Those which furnish the material for conscious sensations and give information as to the position of the limbs, &c., are entirely homolateral, and travel up in the posterior columns of the same side of the cord. All impulses which reach the brain cross finally to the optic thalamus and thence to the cortex of the opposite side.

Hemisection of the cord on one side causes paralysis of the same half of the body below the lesion. Muscular sensibility is also destroyed on this side. On the other side of the body, sensation to heat, cold, pain, and partially to touch, is destroyed. The sensory disturbances however rapidly pass off, and in animals the spinal cord can be hemisected alternately on right and left side at three different levels without causing a lasting anæsthesia, showing that in the absence of the direct paths the sensory impulses may zigzag up the cord and finally reach their destination and affect consciousness.

The only direct unbroken cortico-spinal fibres are those contained in the pyramidal tracts. Motor impulses, which start from the cerebral cortex on one side, pass down that side till they reach the lower part of the medulla. Here the greater number of the fibres cross over in the pyramidal decussation to run down in the crossed pyramidal tract on the other side of the cord. The few fibres which do not cross over in the pyramidal decussation are continued as the direct or anterior pyramidal tract. These however also cross to the other side in their passage down the cord before becoming connected with the anterior cornual cells. Hemisection therefore of the spinal cord in the dorsal region will produce paralysis of motion and loss of or impaired sensation in the parts supplied by the nerves on the same side below the lesion.[1]

A great part of the white matter of the cord is concerned then in maintaining connection between the brain and higher parts of the nervous system and the periphery, through the intermediation of the cells of the grey matter of the cord. Corresponding to this function we find a gradual increase in the number of fibres in the white matter as we ascend from the sacral part of the cord to the medulla, the white matter being continually reinforced as it ascends the cord by fibres establishing connection with the ganglion cells forming the nuclei of the nerve-roots.

Vaso-motor impulses to the limbs travel down the lateral columns of the cord on the same side.

---

[1] It has been recently stated by Schafer that the pyramidal fibres end, not in the anterior cornua but round the cells of the posterior cornua If this be confirmed, it would show that the cortex affected the spinal motor apparatus by attacking its sensory rather than its motor side, so as to save a multiplication of co-ordinating mechanisms

Section 3

THE CORD AS REFLEX CENTRE

In the lower animals, such as the frog, the spinal cord of itself is able to carry out many complex reflex actions. If the skin around the anus of a decapitated frog is stimulated, a sudden extension of both legs is produced, so that the animal leaps away from the stimulus. If a small piece of filter-paper moistened with acetic acid be placed on the inner side of the right thigh, the right foot will be raised and used to wipe away the offending object. If the right leg be held or be cut off, after various fruitless endeavours to remove the irritant with this limb, the left leg may be raised and used for this purpose. These and many other similar experiments show that the spinal cord, separated from the upper part of the nervous system, is capable in the frog of bringing about many highly complex co-ordinated movements, which are apparently purposive, *i.e.* they seem to have a definite object in view; and arguing from experiments, such as the second one we have mentioned, it has been thought that psychical phenomena may accompany these reflex actions. But it must be remembered that *summation* of afferent impulses occurs just as summation of stimuli applied to a frog's ventricle. A single stimulus, too weak to evoke a reflex contraction, may do so if repeated several times. In our experiment, the right leg being unable to remove the offending object, stimulation goes on, and the effect is summated until it is strong enough to spread to the other side of the cord and so set the left leg in motion.

The time taken up in the transmutation of afferent into efferent impulses in the spinal cord may be estimated by measuring the interval that elapses between stimulation of a sensory nerve with a single induction-shock and the resulting muscular contraction, and subtracting from the amount so determined the time taken in the passage of the impulse up and down the nerve-fibres and the latent period of the muscle, the contraction of which is recorded. The reflex time or 'reduced reaction time' measured in this way is found to be about 0·01 second.

A slight stimulus causes reflex contraction only of the limb stimulated. A stronger stimulus causes contraction of the corresponding limb of the other side also, and the effect of a still stronger stimulus may extend to the other two limbs. With this resistance to passage of impulses in the cord across the middle line and longitudinally from one segment to another, we find a corresponding increase in the reflex time.

Effect of strychnine.—If strychnine be injected into the dorsal lymph-sac of a frog, the spinal cord is so affected that the normal resistance to passage of impulses is abolished. The slightest stimulus of the skin now evokes a maximal reflex action, there being no longer any proportionality between the magnitude of the stimulus and that of the reflex effect produced. The minimal reflex time is not diminished, but the smallest stimulus can travel equally well in all directions in the cord. Hence the slightest touch of the skin sends all the muscles into prolonged tetanic contraction, and the frog becomes stretched out with its limbs stiff and rigid.

It has been shown by Sherrington that the most characteristic point about the action of strychnine is that this drug converts inhibitory into motor reflexes Thus when flexion of the knee is excited by stimulation of the pad of the foot, this movement involves not only contraction of the hamstring muscles but also relaxation of the extensors of the knee. After injection of strychnine a similar stimulus applied to the foot causes simultaneous contraction both of extensors and flexors, all the inhibitory phenomena of every co-ordinated muscular reaction being abolished by the drug

Inhibition.—The reflex action normally following a slight stimulus of any part of the body may be completely prevented or inhibited by strong sensory stimulation of some other part. If the optic lobes of a frog be stimulated by putting a crystal of salt on them, or the central end of the right sciatic nerve by means of a faradic current, stimulation of the skin of the left leg with acid produces no effects whatever. A striking parallel instance of this occurs in our daily mental life. Concentration of the attention in any one direction, either by severe pain or through psychical excitement, causes similar stimuli to be quite unheeded, so that in battle a man may be unaware that he is severely wounded until he feels faint or sees blood flowing. We may say, putting the phenomena of the spinal cord into terms of consciousness, that its ganglion cells are so much occupied with the stronger stimulus that they do not notice a weaker stimulus applied to some other part.

Spinal Reflexes in Higher Animals

When we come to the highest animals—monkey and man—there seems to be a striking difference between their spinal cord and that of the frog, in that the reflex actions, which can be carried out by the cord severed from the medulla and brain, are limited to those of the simplest nature. If a man has had his cord crushed in the dorsal region, tickling the soles of his feet will cause him to draw up his legs, although he is perfectly unconscious that his feet are being touched. But beyond one or two simple reflexes of this description, the spinal cord seems to have no power of carrying out co-ordinated acts. It is however difficult in these cases, and in experiments on the spinal cord in mammals, to eliminate the effects of *shock*. After total transverse section of the spinal cord high up, the animal is in a condition of shock, which lasts a considerable time, his vital activities are profoundly depressed, and it may be impossible to evoke even the simplest reflex action by stimulation of any sensory surface below the lesion. But if the experiment be carefully conducted, and the animal be kept alive for a considerable time, the cord little by little recovers its powers, and we then find that the spinal cord of the dog can carry out the most complicated reflex movements without any connection with the higher centres. In a dog whose cord has been divided in the dorsal region, the reflex movements required for micturition, defæcation, impregnation, and parturition may be normally carried out. If the dog, which usually squats on the ground owing to the paralysis of its hinder extremities, be raised on its hind legs by the hands being placed under the fore-legs, and given a little push forwards, the animal may run along for a few steps before it collapses again into a sitting posture. In this case the reflex running movements of the hind legs, carried out by the separated spinal cord, are started by the sudden stretching of the anterior thigh muscles.

The vascular tone in the lower part of the body, which is ost for some time after the operation, is also regained.

Muscular tone.—Every muscle in the body is normally in a condition of slight continued contraction, which is known as muscular tone. If a frog with intact spinal cord be suspended by the jaw, and the nerves going to the lower limb be cut, this limb will hang down straighter than the other in consequence of the abolition of its muscular tone. The same result may be produced if, instead of dividing all the nerves of the limb, only the sensory or only the anterior roots of those nerves be divided. This shows that muscular tone is reflex, and depends for its maintenance on the intact condition of afferent paths, centre, and efferent paths. On the presence of this tone depends the phenomenon known as ‘tendon-reflex’ or knee-jerk. If the leg be allowed to hang loosely and the patellar tendon be struck, the extensor muscles of the thigh contract and raise the leg. This contraction is probably due to the direct stimulation of the muscle by the sudden stretching produced on striking its tendon. If the muscle has lost its tone by disease of the spinal cord, or through section of the afferent or efferent fibres, striking the tendon will no longer stretch the flabby muscle, and the tendon-reflex will be abolished. The mere stretching however is not the only factor, since under these conditions no knee-jerk is produced, however much the muscle may be passively stretched. The impulses descending the nerves to the muscles seem to keep them in a state of wakefulness, ready to respond to the slightest local stimulus. The characters of these reflex tonic impulses are much affected by the influence of other afferent stimuli. Especially interesting is the relation shown by Sherrington to exist between the tonic condition of antagonistic muscles, *e.g.* between the hamstrings and the vastus internus of the quadriceps extensor muscle. Section of the hamstring muscles (so as to relax them), or even section of their nerve, causes at once great increase in the jerk elicited by tapping the patellar tendon. On the other hand the knee-jerk is at once abolished by stretching the hamstring muscles, or by weak stimulation of the central end of the cut nerve to the hamstrings (Fig. 278). Every sensory stimulus which evokes contraction of one set of muscles will therefore produce inhibition of the antagonistic set.

Very great exaggeration of the tendon phenomenon is observed in cases where the pyramidal tracts are degenerated, and indicates a heightened reflex excitability of the lower spinal centres, perhaps reinforced by impulses from the cerebellum.

The value of the tendon phenomena as a means of diagnosis has tended to obscure their great importance in the normal individual. Every joint is protected by inextensible ligaments and by muscles. A sudden strain on a ligament either will have no effect, or will rupture some of its fibres and perhaps injure the adjacent joint surfaces. An ordinary reflex contraction would be powerless to prevent this, since the mischief would be done before the reaction could take place. But the central nervous system confines itself to keeping the muscles awake, so that they themselves may react to any sudden increase in their tension by an equally sudden contraction, which saves the joint before the central nervous system has even become aware of the strain.

Fig. 278

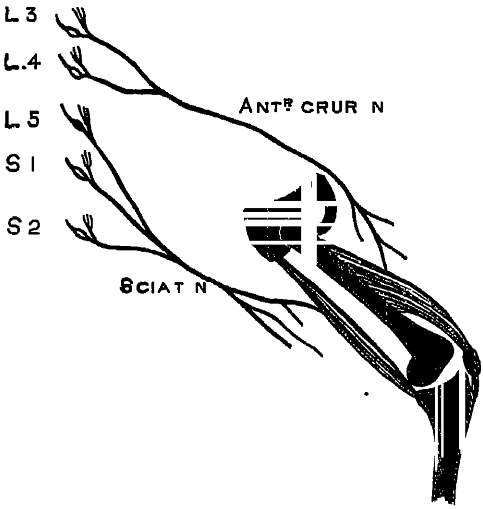


Diagram to show muscles and nerves concerned in Sherrington's experiment on the reciprocal innervation of antagonistic muscles. L.3, L 4, L.5, third, fourth, and fifth lumbar roots, S 1, S 2, first and second sacral roots.

Co-ordination of Movements by the Cord.—Since the act of stretching a muscle in a normal state of tone acts as an excitant, and causes increased tone or even contraction, every movement of a limb, by putting the muscles, antagonistic to the movement, on the stretch, would tend to prevent the carrying out of the movement. Thus flexion of the knee would stretch the extensor muscles and thus increase their tone and resistance to the movement of flexion. Sherrington has shown however that every movement of a limb, worked reflexly, involves not only the contraction of the muscles effecting the movement, but also a simultaneous inhibition of tone and relaxation of the antagonistic muscles, and this occurs in the 'spinal animal,' *i.e.* in one whose spinal centres are entirely cut off from the brain. Thus a 'painful' stimulus, such as the prick of a needle applied to the pad of the foot, causes retraction of the foot, and this movement involves contraction of the flexors and relaxation of the extensors of the limb. On the other hand gentle pressure applied to the pad causes inhibition of the flexors and contraction of the extensors, so that the limb is extended.

The reflex extends also to the other side of the cord, but here the efforts are reversed: extension of the stimulated limb being associated with flexion of the opposite limb, *i.e.* the ordinary association of movements involved in the diagonal action of the limbs in progression.

The spinal cord is thus able to carry out co-ordinated acts of considerable complexity, these acts being adapted to the character and situation of the stimulus, and also to the previous state of activity of the cord and of the muscles involved

Other reflex functions of the cord are concerned with the carrying out of the following actions :—

Micturition.
Defæcation.
Impregnation and parturition.
Vascular tone.

CHAPTER XV

THE BRAIN

Section 1

THE STRUCTURE OF THE BRAIN

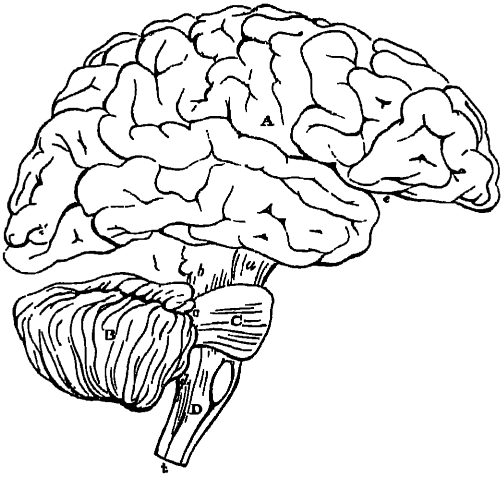
The physiology of the brain falls naturally into two main divisions, viz.—the cerebral hemispheres, and the rest of the brain, including medulla, pons, iter, and corpora quadrigemina, and third ventricle.

This second part may be considered as a prolongation of the spinal cord forwards, consisting like this of a central tube of grey matter, surrounded by a tube of white matter. Owing to the importance and complex connections of the nerve-roots which arise from this part of the neural axis (cranial nerves), the typical division of grey matter into cornua becomes lost; and we find that, while some nerves take their origin from the central tube of grey matter, in other cases the collection of cells forming the nucleus has become more or less separated from the central axis.

Moreover masses of grey matter, which have no representative in the cord, make their appearance in the white matter.

The roof of the neural canal, which over the third ventricle and the posterior part of the fourth is greatly thinned, consisting merely of a layer of epithelial cells, is thickened over the iter (second cerebral vesicle) to form the corpora quadrigemina, and over the pons and anterior part of the fourth ventricle it grows out into a large excrescence with complicated structure—the cerebellum (cf. Fig. 285). Covering the corpora quadrigemina and cerebellum is a layer of grey matter outside a central mass of white fibres. The lateral walls of the third ventricle (first cerebral vesicle) are thickened to form the optic thalami, which contain masses of grey matter. The cerebral hemispheres are formed by hollow outgrowths from the first cerebral vesicle. These in course of development become as large as the whole of the rest of the brain put together, and grow backwards over the rest of the brain as far as the middle of the cerebellum (Figs. 9, 10, pp. 16, 17). Their upper walls become very much thickened, and consist of white matter internally and grey matter externally. Their lower walls remain as a thin layer of undifferentiated epithelial cells, this becomes closely applied to the epithelial layer forming the roof of the third ventricle, from which it is separated only by a process of the pia mater carrying numerous blood-vessels (the velum interpositum). The lower and outer wall of the cerebral hemispheres becomes very much thickened, and forms the corpus striatum, which is closely applied to the front and outer part of the optic thalamus. In it two masses of grey matter are developed, the nucleus caudatus and nucleus lenticularis, separated from one another by a layer of white fibres, which is continuous with a similar layer separating the corpus striatum from the optic thalamus, and is called the internal capsule.

Fig 279

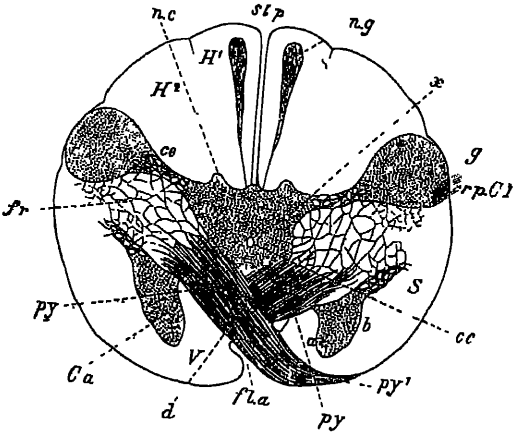


Human brain viewed from the side, to display the various divisions (Quain) A, cerebral hemisphere; B, cerebellum, C, pons Varolii, D, medulla oblongata, *a*, crura cerebri, *b*, superior, *c*, middle, and *d*, inferior peduncles of cerebellum

It will be convenient to trace first the modifications undergone by the axial part of the nervous system in the brain, and then to deal with the new masses of grey matter which have no homologies in the spinal cord, as well as the long tracts of white matter serving to connect different levels or different sides of the brain.

In examining successive sections from the spinal cord up through the medulla, the first change which makes its appearance is due to the decussation of the pyramids

FIG. 280



Section through the lower border of the medulla oblongata, at the pyramidal decussation (Bechterew) *fla* anterior fissure, *d*, decussation of the pyramids, *V*, anterior columns; *Ca*, anterior cornu, *cc*, central canal; *S*, lateral columns, *fr*, formatio reticularis, *ce*, neck, and *g*, head of the posterior cornu; *r p C.1*, posterior root of first cervical nerve, *nc*, beginning of nucleus cuneatus, *ng*, nucleus gracilis, *H*¹, funiculus gracilis, *H*², funiculus cuneatus, *slp*, posterior fissure.

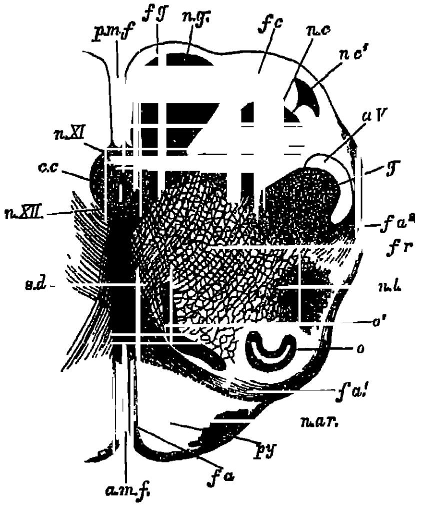
(Fig. 280). Throughout the spinal cord, fibres have been crossing from one side to the other through the anterior white commissure, many of them belonging to the pyramidal system. But at the lower border of the medulla we see a large mass of fibres crossing between the anterior columns and the postero-lateral columns, at first cutting off the head of the anterior horn and later on breaking this up altogether, so that the only definite collection of grey matter left in this situation is a small part of the lateral column of grey matter known as the lateral nucleus. In this way are formed the big anterior columns of the medulla, which are known as the pyramids, and which contain all the fibres that in the cord are represented by the direct and crossed pyramidal tracts.

The next change is due to the ending of the posterior columns. It will be remembered that these are the central ascending branches of dorsal nerve-roots, having therefore an origin outside the cord. All the way up the cord they send in collaterals to end in the grey matter of the posterior horn. The main mass however terminates in the medulla just above the pyramidal decussation in two collections of grey matter—the nucleus gracilis and the nucleus cuneatus, which seem to be formed by a great hypertrophy of the grey matter at the root of the posterior horn. The effect of this development in the dorsal region of the medulla is to push the head of the posterior horn outwards. At the same time this mass of gelatinous substance becomes enlarged, so that in section we have three grey masses from within outwards, the nucleus gracilis, the nucleus cuneatus, and the nucleus of Rolando (Fig. 281).

With the disappearance of the posterior columns and the development of the pyramids we get a practical obliteration of the anterior fissure and a displacement of the central canal towards the dorsal surface. A little higher up the canal opens out altogether, forming the fourth ventricle, covered on its dorsal surface only by a thin layer of ependyma, a simple epithelium representing all that is left of the dorsal wall of the primitive hind brain. The appearance of the section is now modified by two structures. In the first place a new mass of grey matter consisting of a thin layer shaped like a flask with its orifice directed inwards (Fig. 282, *o*) is developed in the lateral part of the medulla, between the pyramids in front and the tubercle of Rolando behind. This is the olivary body, and has on its inner and dorsal sides two other little grey masses which are the accessory olivary bodies. The other feature is the new relay of sensory fibres which start from the dorsal nuclei, the nuclei gracilis and cuneatus. These fibres run outwards and forwards from the nuclei right round the medulla, some passing superficially to the olivary body to join the restiform body of the opposite side, while others pass deeply to the olives, and crossing in the median raphe turn upwards in the broken mass of grey and white matter which lies between the olives and the superficial grey matter of the fourth ventricle. Some fibres also pass into the restiform body of the same side.

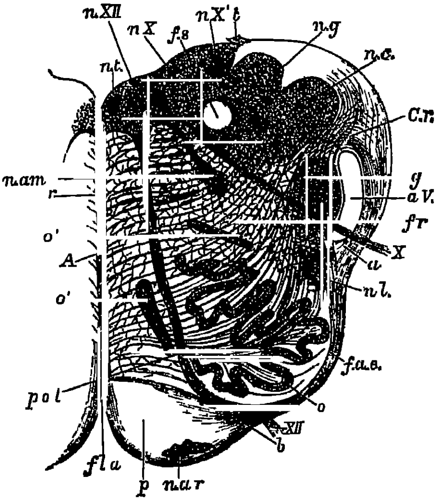
It will be remembered that the anterior half of the fourth ventricle is covered in by the cerebellum, which is attached to the axial part of the brain by three peduncles, the inferior peduncle or restiform body, the lateral peduncles which form the great mass of transverse fibres known as the pons Varolii, and the superior peduncles which run forward to the posterior corpora quadrigemina. The restiform bodies can be

Fig 281



Section of the medulla oblongata in the region of the superior pyramidal decussation (Schwalbe) $\frac{4}{1}$ *a m f*, anterior median fissure; *f a*, superficial arciform fibres emerging from the fissure; *py*, pyramid; *n ar.*, nucleus of the arciform fibres, *f a'*, deep arciform fibres becoming superficial, *o*, lower end of olivary nucleus, *o'*, accessory olivary nucleus, *n.l*, nucleus lateralis, *f r*, formatio reticularis, *f a²*, arciform fibres proceeding from formatio reticularis, *g*, substantia gelatinosa of Rolando, *a V*, descending root of fifth nerve, *n c*, nucleus cuneatus; *n c'*, external cuneate nucleus, *f c*, funiculus cuneatus, *n g*, nucleus gracilis, *f g*, funiculus gracilis, *p m f*, posterior median fissure, *c c*, central canal surrounded by grey matter, in which are *n XI*, nucleus of the spinal accessory, and *n XII*, nucleus of the hypoglossal, *s d*, superior pyramidal decussation (decussation of fillet) regarded as the direct continuation forwards of the postero-lateral columns of the cord, *minus* the pyramidal tracts, the chief remaining tract therefore being the posterior or direct cerebellar tract. In the region of the dorsal nuclei, however, it receives accession of fibres from the gracile and cuneate nuclei of the same side and, through the superficial arcuate fibres, from the nuclei of the opposite side, and thus passes as a thick white bundle into the cerebellum. On its way it is joined by a smaller bundle, the internal restiform body, which conveys fibres from the vestibular division of the eighth nerve and from Deiters' nucleus to the cerebellum.

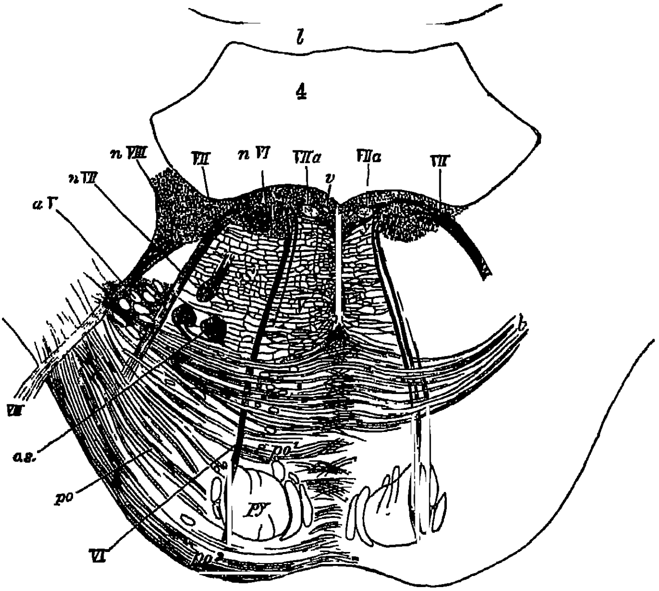
FIG 282



Section of the medulla oblongata at about the middle of the olivary body (Schwalbe) $\frac{4}{1}$ *f l a*, anterior median fissure, *n ar*, nucleus arciformis; *p*, pyramid, *XII*, bundle of hypoglossal nerve emerging from the surface; at *b* it is seen coursing between the pyramid and the olivary nucleus, *o*, *f a e*, external arciform fibres, *n l*, nucleus lateralis, *a*, arciform fibres passing towards restiform body, partly through the substantia gelatinosa, *g*, partly superficial to the descending root of the fifth nerve, *a.V*, *X*, bundle of vagus root, emerging, *fr*, formatio reticularis, *c r*, corpus restiforme, beginning to be formed, chiefly by arciform fibres, superficial and deep; *n c*, nucleus cuneatus, *n g*, nucleus gracilis, *t*, attachment of the tænia, *f s*, funiculus solitarius; *nX*, *nX'*, two parts of the vagus nucleus, *n XII*, hypoglossal nucleus; *n t*, nucleus of the funiculus teres, *n am.*, nucleus ambiguus, *r*, raphe, *A*, formatio reticularis alba, *o'*, *o''*, accessory olivary nuclei, *o*, olivary nucleus, *p o l*, pedunculus olivæ

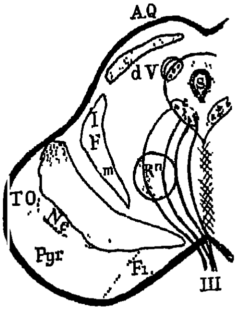
A section through the pons shows the fourth ventricle widely dilated, with a floor formed of grey matter as in the medulla. The chief difference in the appearance of the section is due to the great masses of transverse fibres which pass into the pons by the lateral peduncles of the cerebellum, cross by the median raphe, and either turn upwards or downwards on the opposite side or end in connection with the nerve-cells which are scattered throughout the white fibres. The pyramids can still be seen as thick longitudinal bundles on each side in the midst of the transverse fibres. Dorsally to these transverse fibres is a special mass of grey matter known as the superior olive. Even in the pons we can

FIG 283



Section across the pons at about the middle of the fourth ventricle (Schwalbe) $\frac{3}{1}$ *py* pyramid bundles continued up from the medulla; *po*, transverse fibres of the pons passing from the middle crus of the cerebellum, before (*po*^{1}) and behind (*po*^{2}) the chief pyramid bundles, *t*, deeper fibres of the same set, constituting the trapezium, the grey matter between the transverse fibres is not represented, *r*, raphe, *o s*, superior olivary nucleus, *a V*, bundles of the descending sensory root of the fifth nerve enclosed by a prolongation of the grey substance of Rolando, *VI*, root bundle of the sixth nerve, *n VI*, its nucleus, *VII*, root bundle of the facial nerve, *VIIa*, longitudinal portion of the same, *n VII*, its nucleus, *VIII*, (superior) root of the auditory nerve, *n VIII*, its nucleus; *v*, section of a vein divide the nervous mass, lying below or anteriorly to the central grey matter, into two parts—the formatio reticularis behind and the transverse fibres and pyramids in front. A little further forward a section will escape the cerebellum altogether, and will cut through the fourth ventricle, bounded ventrally by the upper part of the pons and dorsally by the thin mass of grey matter, the valve of Vieussens (Fig. 283). On each side will be seen the superior peduncles of the cerebellum, made up of fibres running from cerebellum to posterior corpora quadrigemina, as well as the continuation upwards of the antero-lateral ascending tract, which passing up in this peduncle bends dorsally round the fourth nerve, and running backwards ends in the superior vermis of the cerebellum.

FIG. 284

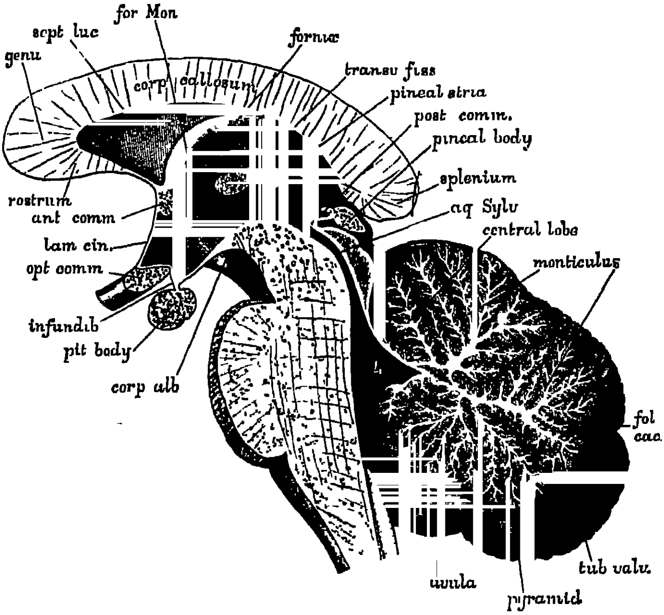


Diagrammatic transverse section through mid-brain to show position of fillet and pyramid A Q Anterior corpus quadrigeminum dV Descending motor root of fifth nerve F Fillet (I, lateral, and m, mesial fillet) Pyr Pyramid Fi Fibres from frontal lobe to pons T O Fibres from occipital lobe to pons Ne. Fibres from nucleus caudatus to pons III Root of third nerve. S Sylvian iter Rn. Red nucleus.

A little further forwards the fourth ventricle comes to an end, and the section passes through the mid-brain, the cavity of the second cerebral vesicle being represented by the narrow Sylvian aqueduct, bounded dorsally by the corpora quadrigemina and ventrally by the crura, the stalks of the brain. The crura are divided by an irregular mass of grey matter, the substantia nigra, into two parts. Anteriorly is the pes or crusta, composed almost entirely of longitudinal white fibres. The dorsal part, the tegmentum, is a direct prolongation forwards of the formatio reticularis of the medulla and pons, and like this contains much scattered grey matter, besides one large, more distinct mass known as the red nucleus.

The cerebral axis comes to an end at the third ventricle, which corresponds to the first cerebral vesicle. It terminates in the following way: the roof ceases to exist, being reduced to a mere layer of epithelium. The floor is also thinned, but still contains nervous matter, forming the optic commissure, the infundibulum, and the corpora albicantia (Fig 285). The lateral wall however undergoes considerable development and forms the great cerebral ganglion known as the optic thalamus. From the front part of the first cerebral vesicle the cerebral hemispheres have been developed, and in the anterior and basal portion of these hemispheres a complicated mass of grey matter, the corpus striatum, has been developed in close proximity to the optic thalamus. As the crura cerebri pass up, the tegmentum becomes continuous with the optic

FIG 285



Portion of a median section of the brain, showing the corpus callosum, third ventricle, iter or aqueduct of Sylvius, fourth ventricle, cerebellum, pons, etc (G D Thane) thalamus and tissues of the subthalamic region, while the crusta diverging somewhat sweeps round the outer surface of the optic thalamus, lying thus between the posterior part of the corpus striatum (the lenticular nucleus) and the optic thalamus. In front the fibres pass as a distinct layer through the substance of the corpus striatum between the nucleus lenticularis and nucleus caudatus of this body. The layer of white matter is thus fan-shaped, and expands still further after passing between the basal ganglia to be distributed to all parts of the cortex of the cerebral hemispheres, forming an important constituent of the white matter, the corona radiata, underlying the superficial grey matter. The part between the basal ganglia is known as the internal capsule (*v.* Figs. 286 and 287). The anterior and posterior parts (in horizontal section) are inclined to one another, so that we can distinguish an anterior and a posterior limb, the junction of the two being known as the genu.

The Axial Grey Matter

In the spinal cord we could distinguish between the anterior grey matter giving origin to the motor nerves, the posterior grey matter serving as an end-station for a number of the sensory posterior root-fibres, and a lateral horn, less well marked, probably giving origin to the visceral system of nerves.

As the central canal widens out to form the fourth ventricle, the relative position of these various parts becomes altered, the anterior grey matter being now nearest the median line, while the posterior grey matter lies more laterally. The lateral grey matter seems to lie deeper than the rest, from which it is separated by a part of the tangle of fibres and cells known as the *formatio reticularis*.

All the cranial nerves from the third to the twelfth arise or end in the axial grey matter, or in close proximity to it. So great however is the complexity of this part of the nervous system, and so involved are the genetic relations of the various nerves, that it is difficult or impossible in many cases to state definitely the spinal analogies of the various nerves.

The cranial nuclei (of origin or termination) may be roughly classed as follows:

1. *Motor nuclei*, close to the middle line in floor of fourth ventricle and iter. From below upwards we get definite groups of large cells giving origin to the fibres of the hypoglossal, sixth nerve, fourth nerve, third nerve

2. *Sensory nuclei*, *i.e.* first cell-stations of afferent fibres having their trophic centres outside the cord. These lie externally to the motor nuclei, and are represented by the combined nucleus of the glossopharyngeal, vagus, and accessory, and also by the nuclei of the eighth nerve and the sensory nucleus of the fifth, with its descending prolongation in the *substantia gelatinosa*.

3. *Nuclei of efferent nerves belonging to the splanchnic system.* These lie more deeply at some distance from the middle line, and include the nucleus ambiguus for the efferent fibres of the vago-glossopharyngeal, the nucleus of the seventh or facial, and probably the motor nucleus of the fifth nerve.

In a cross-section of the medulla at the pyramidal decussation, before the central canal has opened out (Fig. 280), two groups of cells are seen in the central grey matter. The anterior of these consists of large multipolar cells, and gives origin to the motor fibres of the hypoglossal nerve. The posterior group is the lower end of a long column which receives the end-arborisations of the afferent fibres of the ninth, tenth, and eleventh nerves (*glossopharyngeal*, *vagus*, and *bulbar* portion of *spinal accessory*).

In a section a little higher up, taken through the middle of the olivary body (Fig. 282), the central canal has opened out into the fourth ventricle, and the vago-glossopharyngeal is now seen lying laterally to the hypoglossal nucleus. The nerve-fibres connected with these nuclei pass out on either side of the olivary body, the hypoglossal taking the median and the vago-glossopharyngeal the lateral position. The fibres of these afferent nerves, like all others in the bulb or cord, divide into ascending and descending branches on arriving at their grey matter. The ascending branches are short, but the descending extend some distance down the medulla, as a special bundle, the *funiculus solitarius*, lying immediately under the vago-glossopharyngeal nucleus. This bundle is sometimes called the descending sensory root of the glossopharyngeal, or, from its supposed importance for the respiratory centre, the *respiratory bundle of Gierke*.

The motor fibres of the vago-glossopharyngeal, which are splanchnic in function, arise from a mass of grey matter lying deeply in the medulla, and corresponding apparently to the lateral horn. This nucleus is known as the *nucleus ambiguus* (*n.am.*, Fig. 282).

At the upper part of the medulla, where the fourth ventricle attains its greatest diameter, the important eighth nerve enters (Fig. 295, p. 639). This really consists of two nerves, an outer division derived from the cochlea and carrying auditory sensations, and an inner division derived from the vestibule and semicircular canals and conveying afferent impressions which determine the maintenance of equilibrium. These nerves are purely sensory, and are derived from bipolar cells situated in the internal ear. As they enter the medulla they are separated by the mass of white fibres forming the restiform body. Both sets of fibres bifurcate on entering the medulla. The branches of the cochlear nerve make connection with two collections of cells, the dorsal nucleus, apparently embedded in the fibres of the root itself, and the accessory nucleus, a little triangular mass of grey matter situated in the angle between the cochlear and vestibular nerves. From these nuclei fibres are given off which take two courses. Some, following the previous course of the cochlear nerve, pass across the surface of the fourth ventricle as the *striæ medullares* or *striæ acousticæ*, and then bending inwards pass into the tegmentum of the opposite side. Others pass deeply and form a mass of transverse fibres in the ventral part of the tegmentum, known as the *corpus trapezoides*. After making connections with the superior olivary body and a special nucleus, they join the superficial set of fibres, and pass up in the tegmentum to the inferior corpora quadrigemina, forming the lateral fillet.

The *vestibular nerve* also has two nuclei of termination, the *median nucleus* with small cells, and the *lateral* or *Deiters' nucleus* with large cells. The descending fibres end chiefly in the median nucleus, while the ascending fibres end in Deiters' nucleus. From the latter a distinct band of fibres passes up to the cerebellum, forming the median division of the restiform body, while other fibres run across to the tegmentum of the opposite side, where they take part in the formation of the *posterior longitudinal bundle*.

In a section through the fourth ventricle through the middle of the pons, a group of large cells is seen in the position occupied by the nucleus of the hypoglossal below. In this situation however these cells give rise to the fibres of the sixth nerve. Another group is seen lying laterally and more deeply, evidently belonging to the lateral horn system. This is the nucleus of the seventh or facial nerve, the fibres of which pass dorsally and anteriorly, looping round the sixth nerve-nucleus, before issuing as the root of the seventh nerve.

In the upper part of the pons we find the big fifth nerve with its two roots. The fibres of the sensory root derived from the cells of the Gasserian ganglion bifurcate. The upper divisions, which are short, end in a mass of grey matter at the lateral part of the *formatio reticularis*, the so-called sensory root, while the descending divisions form a long strand of white fibres passing down as far as the second cervical nerve. They form a sort of cap to the *substantia gelatinosa* of Rolando, around the small cells of which the fibres finally terminate. The motor fibres arise partly from the motor nucleus, a mass of cells lying internally to the sensory nucleus and belonging probably to the lateral horn system. A large number however are derived from a long column of cells, which stretches forward from the nucleus as far as the level of the anterior corpora quadrigemina. These fibres are known as the descending motor root of the fifth nerve.

In the region of the mid-brain, besides the root of the fifth nerve just mentioned, we find only the motor nuclei of the fourth and third nerves, which are situated near the median line in the ventral part of the central grey matter, corresponding in situation to the sixth and twelfth nerves lower down.

Intermediate Grey Matter of the Cerebral Axis

The masses of grey matter which are found throughout this region may be regarded as extra shunting stations (or association centres for various systems of nuclei and conducting paths), which have arisen in consequence of the great complexity of reaction required of the nerve mechanisms in connection with the organs of special sense. We must confine ourselves here to little more than the enumeration of some of the chief masses, though we shall have occasion to refer to some in more detail when dealing with the co-ordinating mechanisms of the cerebral axis. From below upwards we may enumerate the following grey masses :

In the medulla is the large *olivary body*, with the *accessory olive* lying on its inner side. Each olive sends fibres across the middle line to the opposite cerebellar hemisphere, and must be regarded as connected with this body in its functions, since atrophy or removal of one side of the cerebellum is followed by atrophy of the opposite olive.

In the pons we find a similar but smaller body, the *superior olive*, in the neighbourhood of the nucleus of the seventh nerve. The superior olive is closely connected with the co-ordination of visual and vestibular impressions with the eye movements (Fig. 290)

Deiters' nucleus, which occurs in the same region, although described as one of the nuclei of the eighth nerve, might equally well be included in this class owing to its manifold connections with both afferent and efferent mechanisms.

In close connection with Deiters' nucleus are a number of grey masses in the cerebellum, the so-called *roof-nuclei* in the roof of the fourth ventricle, and the *dentate nucleus* in the middle of each cerebellar hemisphere.

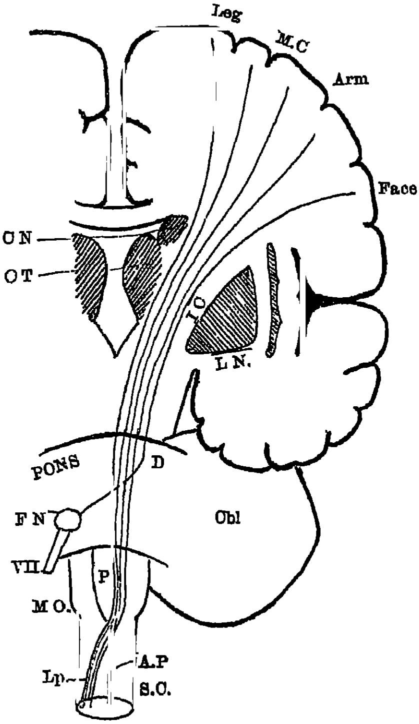
In the mid-brain we must mention the superficial grey matter covering the corpora quadrigemina.

On the ventral side of the Sylvian iter are various masses of grey matter in the crura, the *red nucleus*, a large mass in the tegmentum just below the oculo-motor nucleus, and the *substantia nigra*, which divides each crus into two parts, the dorsal *tegmentum* and the ventral *pes* or *crusta.*

Finally at the fore part of the cerebral axis we come to the two great ganglionic masses already described, the *optic thalamus* and the *corpus striatum.* The optic thalamus is connected by fibres with all parts of the cortex and represents the termination of the whole tegmental system, so that in many ways it may be regarded as a sort of foreman of the central nervous system, bringing all parts of this system in relation with the supreme cerebral cortex.

The corpus striatum on the other hand represents the most primitive part of the cerebral hemispheres. It does not act as the intermediary between the cortex and the lower parts of the brain, but its fibres run to lower levels in company with those from the cortex. It seems possible that it may under conditions carry out in a simple way the functions which, with more elaboration, need the co-operation of the cortex.

FIG. 286.



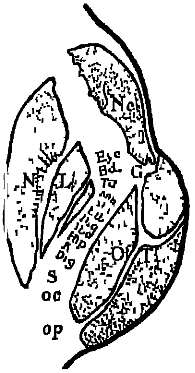
Diagrammatic vertical section through brain showing course of pyramidal fibres M C Cortex on which are situated the motor centres I C Internal capsule C N Caudate nucleus. O T Optic thalamus L N Lenticular nucleus D Point of decussation of fibres to F N, facial nucleus VII Seventh nerve. P Pyramids of medulla A P Anterior pyramidal tract Lp Lateral pyramidal tract. M O Medulla oblongata S C Spinal cord Cbl Cerebellum

The Connecting Tracts of the Brain

The tracts of the white matter of the brain may be divided into the *longitudinal tracts* which connect different levels of the brain with one another, and the *commissural* or *transverse* *tracts* which run across from one side of the brain to the other and serve to connect the two sides of the brain at the same level. The longitudinal tracts may be divided into those contained in the crusta or pes and its continuations, and those which run in the tegmentum.

The Pedal System.—The most important of these tracts is the *pyramidal tract* of fibres which, arising from cells in the central portion of the cerebral cortex (the motor area), pass along the corona radiata and converge to form the genu and anterior two-thirds of the posterior limb of the internal capsule. The arrangement of fibres in the internal capsule according to their function is indicated in Fig. 287. Thence they pass through the crura cerebri, taking up the middle two-thirds of the crusta, and then through the pons. Emerging from the lower border of the pons, they form two thick masses, the anterior pyramids of the medulla. At the lower part of the medulla, the major portion of the fibres passes across to the posterior part of the lateral column of the other side, and is continued down this side as the crossed pyramidal tract. A small number of fibres of each tract do not cross at once, but pass down in the cord in the same situation as they occupied in the medulla, forming the direct

FIG 287.

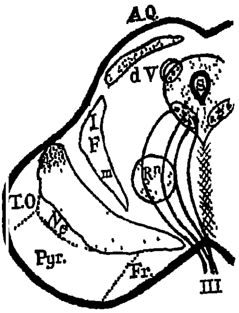


Horizontal section through basal ganglion to show arrangement of fibres in internal capsule From before backwards the fibres go to the motor centres for the eye, head, tongue, mouth, shoulder, elbow, fingers, abdomen, hip, knee, and foot S Fibres from temporo-occipital region oc Fibres to occipital lobe op Optic radiations. Nc Nucleus caudatus. O T Optic thalamus N L Nucleus lenticularis (After Sherrington) or anterior pyramidal tracts. These however also cross gradually in the cord before reaching their final destination—the anterior cornu of the opposite side.

The anterior limb of the internal capsule in front of the genu is occupied by the *frontal cortical* fibres, which are derived from the grey matter of the frontal lobes and which proceed along the innermost portion of the crusta to the pons, where they end, probably in indirect connection with the transverse fibres of the middle peduncle of the cerebellum.

Immediately behind the pyramidal tracts in the posterior limb of the internal capsule is a collection of fibres (the *temporo-occipital cortical*) which run from the temporo-occipital convolutions of the cortex through the internal capsule and along the outer lateral border of the crusta to end in the pons in the same manner as the frontal fibres just described.

FIG 288



Transverse section through mid-brain to show position of fillet and pyramid A Q Anterior corpus quadrigeminum dV. Descending root of fifth nerve F Fillet (l, lateral, and m, mesial fillet) Pyr Pyramid Fr Fibres from frontal lobe to pons T O Fibres from occipital lobe to pons Ne Fibres from nucleus caudatus to pons III. Root of third nerve S Sylvian iter Rn Red nucleus.

A fourth constituent of the crusta, which does not appear in the internal capsule, is the small band of fibres derived from the caudate nucleus of the corpus striatum. These firbes seem to end partly in the substantia nigra itself and partly, along with the others of this system, in the pons Varolii.

The Tegmental System.—Whereas the pedal system consists of fibres which for the most part degenerate downwards

Fig. 289

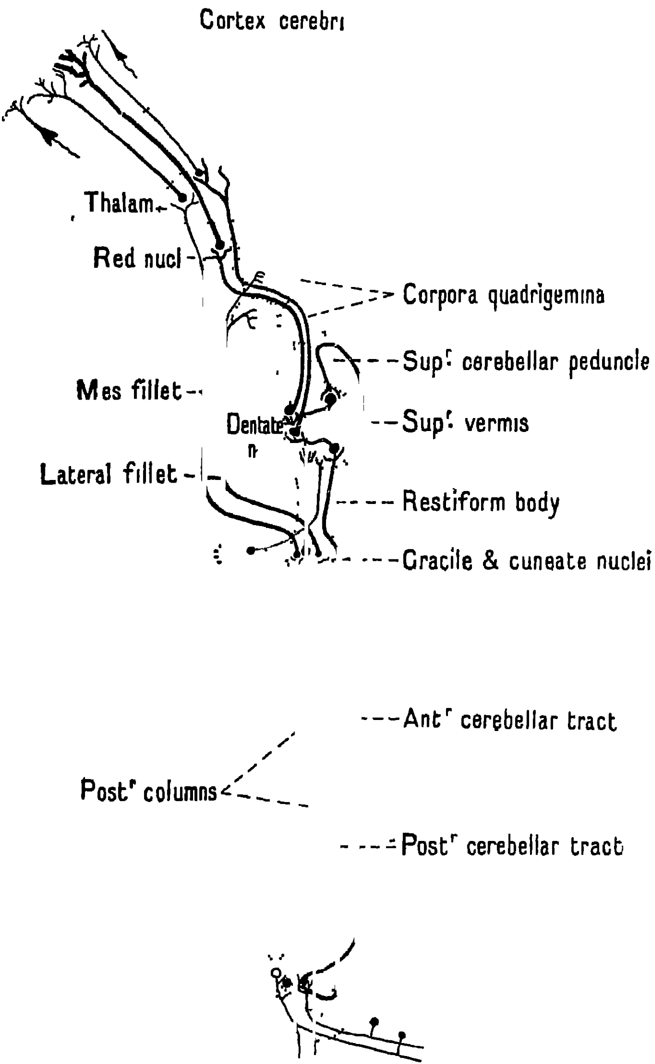


Diagram to show possible paths of afferent impulses from posterior roots to cerebral cortex. The fillet path is represented in black, the cerebellar path in red.

and, in the case of the pyramidal tracts at any rate, carry efferent impulses, the tegmentum furnishes the various alternative paths for afferent impulses on their way to the cerebral hemispheres.

Two main courses are open for these impulses (Fig. 289). They may travel (1) by the dorsal column nuclei and tract of the fillet or (2) indirectly through the intermediation of the cerebellum.

1 *The fillet path.*—The posterior nerve-roots send direct continuations into the posterior columns of the cord. The fibres in these columns end by arborisations round the cells of the gracile and cuneate nuclei. From these cells fresh relays arise which cross as the internal arcuate fibres to the inter-olivary layer on the other side of the medulla in the supra-pyramidal or sensory decussation. Hence they pass up in the tegmental region of the pons and in the tegmentum of the crus as a flat band of fibres—the *fillet*, which divides into two portions known as the lateral and median divisions. The lateral fillet is formed almost entirely by fibres from the cochlear nucleus and ends in the corpora quadrigemina. The median division, which receives also accessions from the sensory nuclei of the bulb, ends partly in the grey matter of the anterior corpus quadrigeminum, the great majority of the fibres however passing to the thalamus itself. From the thalamus fibres proceed to the frontal and parietal cortex through the extreme anterior end of the internal capsule, while others pass through the posterior third of the hind limb to be distributed to all parts of the temporal and occipital lobes. The latter fibres, which are associated with others derived from the anterior corpus quadrigeminum and concerned largely with the passage of visual impulses, are often spoken of as the *optic radiations.*

2. *The cerebellar path.*—The posterior roots, as they enter the cord, send collaterals to arborise round the cells of Clarke's column and other cells of the grey matter. From these cells fibres arise which form the anterior and posterior cerebellar tracts. The anterior (antero-lateral ascending) tract passes up in the lateral columns through the pons into the superior peduncle of the cerebellum, where it loops round to end in the superior vermis. The posterior (direct) cerebellar tract also passes up into the superior vermis of the

cerebellum by the restiform body. By the same path the cerebellum also receives fibres from the gracile and cuneate nuclei of both sides.

The continuation forwards of these impulses is by means of the superior cerebellar peduncles, which, arising chiefly in the dentate and roof nuclei but also to a certain extent in the superficial grey matter of the cerebellum, pass forwards to the corpora quadrigemina. Converging below these bodies they decussate, and finally end in the tegmentum, chiefly in connection with the red nucleus. The further continuation to the cerebral hemispheres must lie in the tracts already described connecting them with the tegmentum.

Fig 290.

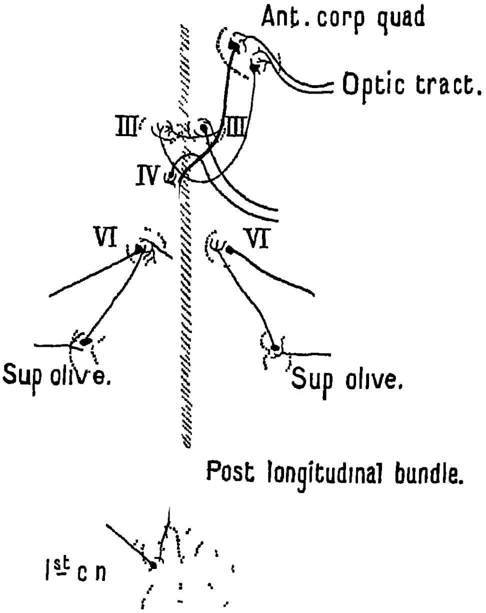


Diagram to illustrate some of the connections of the nuclei of the nerves to the ocular muscles (after Held)

The *posterior longitudinal bundle* (Fig. 290) is a distinct tract of white fibres lying dorsally to the reticular formation. In front it runs just below the oculo-motor nucleus, with which it is connected, and can be traced backwards (or downwards) as far as the first cervical nerve, where it merges in the ground fibres (anterior basis bundle) of the anterior columns. It is made up partly of descending fibres from the anterior corpus quadrigeminum and nuclei of the floor of the third ventricle, partly of ascending fibres from the various sensory nuclei of the medulla. One of its chief functions is to serve as a means of communication between the various oculo-motor nuclei (third, fourth, and sixth nerves) around the cells of which many of its fibres end.

The Commissural Fibres of the Central Nervous System

The chief mass of these is contained in the corpus callosum which connects the two opposite cerebral hemispheres.

Other smaller commissures are the anterior white commissure connecting chiefly the olfactory lobes and temporo-sphenoidal convolutions, and the posterior commissure between the two thalami.

The great mass of transverse fibres forming the pons, which serve to connect the cerebellar hemispheres, are not directly continuous across the middle line but, starting from the superficial grey matter of one hemisphere, end in the grey matter of the opposite side of the pons.

SECTION 2

SUMMARY OF THE CONNECTIONS AND FUNCTIONS OF THE CRANIAL NERVES

Cranial nerves.—The cranial nerves are generally reckoned as twelve in number: 1st, olfactory; 2nd, optic; 3rd, oculomotor; 4th, or trochlear; 5th, or trigeminus; 6th; 7th, or facial; 8th, auditory; 9th, glossopharyngeal, 10th, vagus or pneumogastric; 11th, spinal accessory; 12th, hypoglossal.

Of these the first two stand on a different footing from the rest which, like the spinal nerves, are outgrowths of nerve-fibres from the central tube of grey matter surrounding the neural canal or from ganglia corresponding to the spinal posterior root-ganglion. The olfactory and optic nerves are not peripheral nerves at all, but are actual outgrowths from the brain. The olfactory bulb and the retina are morphologically distinct lobes of the brain.

The *first* or *olfactory nerve* (or, more properly, olfactory lobe) has ten or twelve filaments, which pierce the cribriform plate, and are distributed to the olfactory mucous membrane. It is the central organ of smell. It is supposed that impulses do not cross from one side of the body to the cerebral hemisphere of the opposite side, as is the case with all the other nerves of the body.

The *second* or *optic nerve* subserves the function of vision, and that alone. The two nerves join at the *optic chiasma.* Here there is a partial exchange of fibres, and each of the optic tracts, which are the continuations behind the chiasma of the optic nerves, contains fibres from both optic nerves.

Thus the right optic tract contains the fibres from the external half of the right retina and the internal half of the left retina. Since these are corresponding parts of the two retinæ, and are excited by light coming from the left of the person, section of one optic tract causes blindness on the opposite side (*hemianopia*). Each optic tract is connected behind with the back part of the optic thalamus (pulvinar), the external corpus geniculatum, and the anterior corpus quadrigeminum of the same side (Fig. 291). From these points fibres pass through the posterior part of the internal capsule and corona radiata ('*optic radiations*') to the cortex of the occipital lobe.

The fibres forming the optic tracts are the axons of the nerve-cells in the ganglion-cell layer of the retina. Section of the optic nerve therefore is followed by degeneration of these fibres in a central direction. Mixed up with these fibres however are others which run in a centrifugal direction, starting from cells in the optic thalamus or adjacent masses of grey matter and terminating in the inner nuclear layer of the retina (Fig. 292).

Fig. 291.

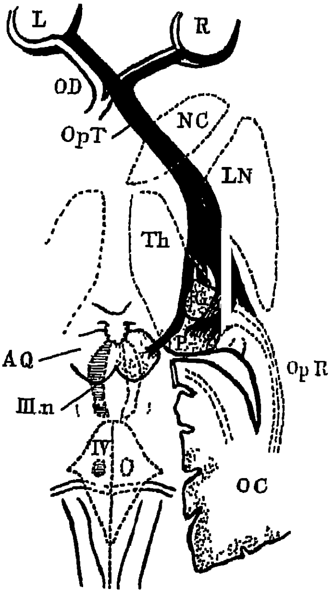
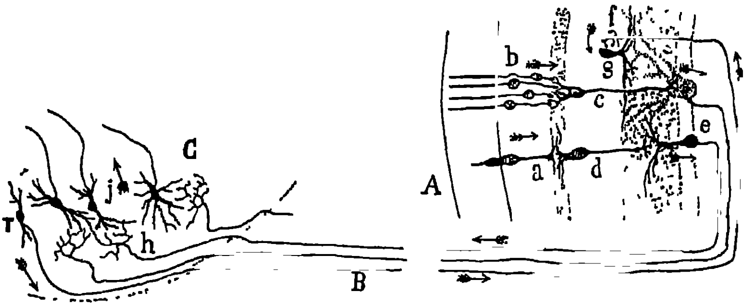


Diagram to show connections of optic tracts (after Sherrington). L, left, and R, right retina OD. Optic decussation (chiasma). OpT. Optic tract. NC. Nucleus caudatus. LN Lenticular nucleus Th. Optic thalamus G External geniculate body. A Q Anterior corpus quadrigeminum P. Pulvinar OpR. Optic radiations running to O C, the occipital cortex III.n. Nucleus of 3rd nerve in floor of Sylvian aqueduct IV Fourth ventricle

The *third* or *oculo-motor nerve* arises from a column of nerve-cells situated at the extreme hind part of the floor of the third ventricle, and from the front part of the floor of the aqueduct of Sylvius, below the anterior corpus quadrigeminum. It emerges from the inner side of the crus cerebri. It is the motor nerve for the levator palpebrarum, superior, inferior, and internal recti, and inferior oblique muscles. It also supplies the constrictor iridis and the ciliary muscle. Stimulation of it therefore causes the eye to look upwards and inwards, with contraction of the pupil and spasm of accommodation. By careful stimulation of various parts of its nucleus the different movements of these muscles may be produced separately.

The nucleus of the *fourth nerve* is situated just behind that for the third in the floor of the Sylvian aqueduct. The fibres run from here round the aqueduct, and take their superficial origin from the valve of Vieussens, a thin plate of grey matter forming the roof of the fourth ventricle just in front of the cerebellum.

Fig. 292



Schema of the course of the visual impulse from rods and cones to brain (Bechterew after Ramón y Cajal) A, retina, B, optic nerve; C, external geniculate body. *a*, cone, *b*, rods, *c*, *d*, bi-polar cells, *e*, ganglion cells; *f*, centrifugal fibre, *g*, spongioblast; *h*, terminal ramifications of retinal nerve-fibres; *j*, cells transmitting impulse to cortex; T, cell giving off centrifugal fibres

This nerve supplies only the superior oblique muscle of the eyeball.

The *fifth* or *trigeminus* resembles a spinal nerve in that it has a motor as well as a sensory root, the latter being provided with a ganglion (Gasserian ganglion). It has a very extensive origin, owing to the fact that its sensory part represents the sensory roots of all the motor cranial nerves from the third to the hypoglossal The middle or motor root arises from a collection of nerve-cells in the floor of the fourth ventricle. It also receives fibres from the descending motor root, which can be traced forwards from the nucleus as far as the level of the anterior corpora quadrigemina.

The sensory root may also be traced into a nucleus lying lateral to the motor nucleus, though in this case the fibres of the nerve end in the nucleus, having their trophic centre in the cells of the Gasserian ganglion. Connected with the sensory nucleus is the descending root of the fifth nerve, which can be traced downwards through the medulla as far as the level of the second cervical nerve, where it appears as a little cap of white fibres on the mass of gelatinous substance forming the head of the posterior horn, and known in the medulla as the tubercle of Rolando.

FIG. 293

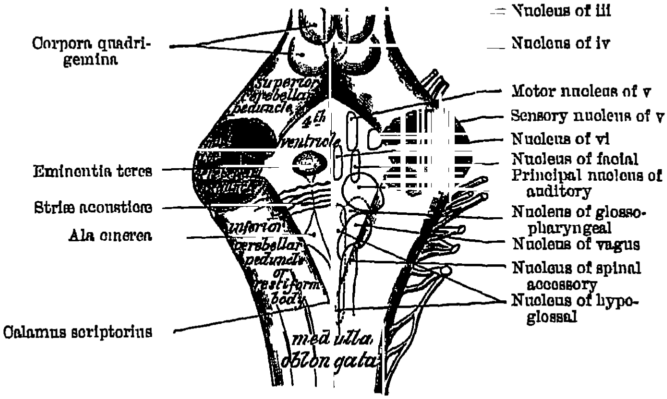


Diagram of fourth ventricle and adjacent parts, as seen from dorsal aspect, to show positions of nerve nuclei. These are marked on the right-hand half. (After Erb)

This nerve is the motor nerve for the muscles of mastication, and for the tensor tympani and tensor palati It is the sensory nerve for the whole of the face (including eyeball, mouth, and nose). It also contains dilator fibres to blood-vessels derived from the chorda tympani, and is said to have *trophic* functions. The latter conclusion is from the fact that section of the fifth nerve in the skull is followed by ulceration and sloughing of the cornea, and finally destructive changes involving the whole eyeball. Since however these results may be prevented by carefully shielding the eye from all dust and deleterious influences, it is probable that the ulceration is merely a secondary consequence of the anæsthesia. The cornea being anæsthetic, foreign objects that fall on its surface are allowed to remain there, and so give rise to injurious changes and ulceration.

The fifth is also said to be the nerve of taste for the anterior third of the tongue, but it is possible that the taste-fibres which run in the fifth are derived from the glosso-pharyngeal.

Fig. 294

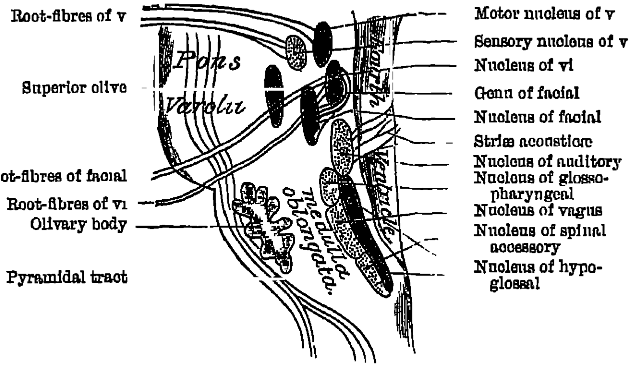


Diagram to show positions of principal nerve nuclei in pons and medulla, side view The organ is supposed to be split down the middle line and the right half viewed from the mesial side. The most mesially situated nuclei are shaded, the others stippled. (After Erb)

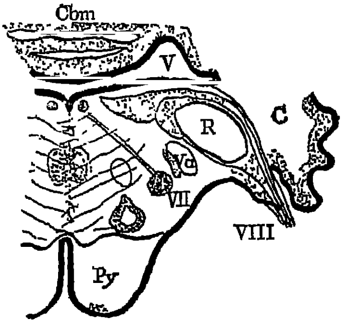
The *sixth* nerve, the motor nerve for the external rectus, rises from a small group of cells in the floor of the fourth ventricle near the middle line.

The nucleus for the *facial* or *seventh* nerve is situated more deeply and laterally than the preceding. It supplies all the muscles of the face, and is therefore the nerve of expression.

The chorda tympani, which is a branch of this nerve, contains secretory and vaso-dilator fibres for the submaxillary gland. The fibres of taste which are said to run in this nerve are probably derived from the glosso-pharyngeal.

The *eighth* or *auditory* rises on a level with the hind margin of the pons by two roots, one of which, the dorsal root, winds round the restiform body, while the other, the ventral or median root, sinks into the substance of the bulb to the inner side of the restiform body. The fibres composing the dorsal roots come from the cochlea and convey sensations of sound. The fibres bifurcate, the ascending branches ending in the dorsal nucleus (acoustic tubercle), while the descending make connection with a mass of cells in the angle between the two roots, known as the accessory nucleus. The ventral root consists of fibres derived from the vestibule and semicircular canals, and carries impulses connected with the reflex maintenance of equilibrium. It ends partly in the lateral auditory nucleus (of Deiters), whence a number of fibres pass up with the restiform body into the cerebellum, and partly in the median nucleus.

FIG. 295.



Section through medulla just behind the pons, to show origin of auditory nerve Cbm Cerebellum. V Fourth ventricle R. Restiform body Py. Pyramid Va. Ascending root of fifth nerve. VII Nucleus of seventh nerve VIII. Auditory nerve

The ninth, tenth, and eleventh nerves are connected with an elongated nucleus in the lateral part of the lower half of the fourth ventricle, the motor fibres of the first two nerves arising from the nucleus ambiguus.

The *ninth* is probably a pure sensory nerve, and conveys sensations from tongue (taste?) and pharynx. Running in it are also motor fibres to the stylo-pharyngeus and middle constrictor of the pharynx.

The *tenth* or *vagus* is joined by the accessory part of the spinal accessory, so that the two nerves may be considered together. It has both afferent and efferent functions, most of which we have already considered.

Efferent functions.

Motor to levator palati and three constrictors of pharynx.
Motor to muscles of larynx.
Inhibitory to heart.
Motor to muscular walls of œsophagus, stomach, and small intestine.
Motor to unstriated muscle in walls of bronchi and bronchioles.
Secretory to glands of stomach and possibly to pancreas.

Afferent functions:

Regulate respiration. Stimulation of central end may quicken respiration and promote inspiration, or may inhibit inspiration. Stimulation of central end of superior laryngeal causes stoppage of inspiration, expiration, cough.
Depressor (from heart to vaso-motor centre).
Reflex inhibition of heart.

The external branch of the *spinal accessory* is the motor nerve of the sterno-mastoid and trapezius muscles.

The *hypoglossal* (*twelfth* nerve) arises from a nucleus in the floor of the fourth ventricle at its lower end close to the middle line.

It is a pure motor nerve, and supplies the intrinsic and extrinsic muscles of the tongue.

Since the integrity of the nuclei of the cranial nerves is a necessary condition for the carrying out of various reflex acts in which these nerves are involved, the grey matter of the fourth ventricle and aqueduct is often spoken of as if it were cut up into a series of centres distinct for every act. It must be remembered however that, when a dozen or more centres are enumerated as being situated in the fourth ventricle, it is not meant that we can anatomically distinguish a group of cells for each act or group of actions named. When we say that a part of the nervous system is a centre for any action, we merely mean that this part forms a necessary link, or meeting of the ways, in the complicated directing of nerve impulses that takes place in every co-ordinated act.

The chief centres are the respiratory and the vaso-motor. These we have already considered. Other centres that may be enumerated are—

Centres for movements of intrinsic and extrinsic ocular muscles.
Cardiac inhibition.
Mastication, deglutition.
Sucking.
Convulsive (connected with respiratory).
Vomiting.
Diabetic (connected with vaso-motor, *v* p. 492).
Salivary.
Centres of phonation and articulation.

SECTION 3

FUNCTIONS OF THE CEREBRAL AXIS

We have already studied the phenomena exhibited by an animal (frog) possessing spinal cord alone. We can now by a study of the same or a higher animal, deprived only of its cerebral hemispheres, come to some conclusion concerning the functions of the lower parts of the brain and, by comparison of these phenomena with those exhibited by an intact animal, of the cerebral hemispheres themselves.

When a frog's cerebral hemispheres have been excised, a casual observer would not at first notice anything abnormal about the animal He sits up in his usual position, and on stimulation may be made to jump away, guiding himself by sight, so that he avoids any obstacles in his path Movements of swallowing and breathing are normally carried out. The animal, thrown on to his back, immediately turns over again. If put into water, he swims about until he comes to a floating piece of wood or any support, when he crawls out of the water and sits still. If he be placed on a board and the board be inclined, he begins to crawl slowly up it, and by gradually increasing its inclination he may be made to crawl up one side and down the other. But a striking difference between him and a normal frog is the almost entire absence of spontaneous motion—that is to say, motion not reflexly provoked by changes *immediately* taking place in his environment. All psychical phenomena seem to be absent. He feels no hunger and shows no fear, and will suffer a fly to crawl over his nose without snapping at it. 'In a word, he is an extremely complex machine, whose actions, so far as they go, tend to self-preservation; but still a *machine* in this sense, that it seems to contain no incalculable element. By applying the right sensory stimulus to him, we are almost as certain of getting a fixed response as an organist is when he pulls out a certain stop.' [1]

The effects of ablation of the cerebral hemispheres of the pigeon are very similar. If left to itself, the bird remains perfectly still and seems fast asleep; if stimulated, it may be made to fly normally, and is then observed to avoid obstacles, guided by the sense of sight. Like the frog, it shows no signs of fear or hunger, and will starve to death on a heap of corn, although it will begin to eat the corn if its beak be plunged into it. In the higher mammals ablation of the cerebral hemispheres produces such severe shock that nothing can be said with regard to the working of the lower part of the brain. The rabbit however will survive the operation for a few hours, and during this time it can be made to run, and no symptoms of paralysis are observed. When a sensory surface or nerve is stimulated, the animal gives forth a prolonged and plaintive cry. We thus see that the axial parts of the brain, together with the corpora quadrigemina and cerebellum, contain all the necessary nervous mechanisms for the carrying out of the co-ordinated muscular actions involved in standing, running, flying, mastication, deglutition, and expression of the emotions.

---

[1] James, 'Psychology.'

Co-ordination of Muscular Actions

The first two of these functions must be considered a little more fully The maintenance of equilibrium depends on a series of complex reflex acts, which are dependent on incoming or afferent impulses, on various centres or interlacements of nerve-paths in the grey matter, and on efferent impulses to the muscles.

The chief afferent impulses which guide the maintenance of equilibrium are those from the skin, eyes, semicircular canals, and muscles themselves. The importance of impulses from the skin is shown by those cases in which, from disease of the sensory tracts, there is anæsthesia of the soles of the feet In these cases the patient is unable to stand with his eyes shut, and indeed may first discover that anything is wrong with him from the fact that he is apt to fall down whenever he is washing his face. The same effect may be experimentally produced by freezing the soles of the feet, so as to make them anæsthetic. If in a brainless frog the skin be stripped from the hind limbs, it no longer sits up in a normal posture, and is unable to climb up an inclined board.

The use of visual impulses in guiding the nervous centres in the maintenance of equilibrium is shown by the preceding experiment, in which no loss of equilibrium occurred till the patient closed his eyes. Sudden destruction of the eye in pigeons or rabbits causes these animals to spin round and round in a circle, or may cause them to fall over. The giddiness too, that is often produced by looking at rapidly moving objects, such as a train or waterfall, shows the connection of this sense with equilibration.

By far the most important afferent impulses are those coming from the semicircular canals. A full account of the effects of interference with these structures has been already given in the chapter on the organs of special sense, where too the intimate connections of the semicircular canals with the movements of the eyes and head have been described.

Finally, all the muscular actions required for the maintenance of equilibrium are guided and regulated by afferent impulses from the muscles themselves. The muscular sense however is still more important in the co-ordination of the muscular contractions by which locomotion is carried out. This is well exemplified in certain cases where, owing to disease of the intra-muscular afferent nerves, or of the sensory channels of the cord, there is a loss of muscular sense accompanied by loss of muscular tone and tendon reflexes. Such cases are said to suffer from ataxy. There is no proportionality between the contractions of the various muscles used, so that some muscles act too strongly and others too feebly. In this way a vast amount of energy is expended with very little practical effect in moving the patient along.

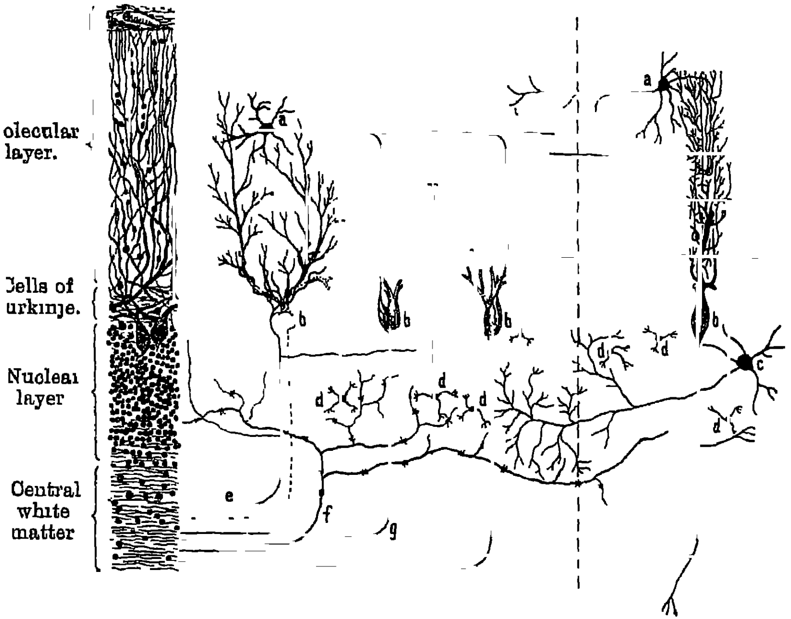
It is difficult to say that the function of co-ordinating movements or maintaining equilibrium is limited to any distinct part of the cerebro-spinal axis. We have already seen that all the machinery necessary for carrying out some of the most complicated movements of locomotion is present in the spinal cord; and it is probable that under normal circumstances all that the higher centres do is to set this machinery going. We may say that these functions are served by the whole cerebro-spinal axis from the third ventricle to the lower end of the spinal cord, together with the outgrowths forming the corpora quadrigemina and the cerebellum. There is a good deal of evidence connecting the latter organ more closely with the co-ordination of movements than with any other function. We may therefore take this opportunity of considering the chief points in the structure and connections of this organ, as well as some subsidiary co-ordinating mechanisms in close connection with the cerebellum.

CEREBELLUM

Structure.—As we have already seen, the cerebellum is formed by an outgrowth from the dorsal wall of the anterior part of the fourth ventricle, and consists of a superficial layer of grey matter enclosing white matter. It is divided into three lobes, two lateral lobes, and one middle lobe forming the superior and inferior vermis The surface of the cerebellum is increased by being thrown into leaf-like folds, so that a section of this organ has a tree-like appearance. A section through a lamina shows three distinct zones —an outer molecular presenting a granular appearance with a few nuclei, internal to this, a granular layer composed of many nuclei of nerve-cells; and most deeply a central core of white matter. Between the molecular and granular layers are situated the cells of Purkinje, large flask-shaped cells each with one apical dendrite, distinguished above all other dendrites of the central nervous system by the richness of its branching, and with one axon, which leaves the base of the cell and passes down into the central white matter, giving off collaterals in its course.

In preparations made by Golgi's method we are able to distinguish the various elements composing these layers and their relations. The molecular layer, besides neuroglia cells and the branching dendrites of the cells of Purkinje, contains certain star-shaped cells (a, Fig. 296), which give off an axon running parallel with the surface in the molecular layer From this axon branches dip down towards the cells of Purkinje, where they end in a rich basket-work of fibres around the body and beginning of the axon of these cells. The nuclear layer presents two kinds of cells. The most numerous is a small cell with a few short dendrites, each of which terminates in a claw-shaped arborisation, and a single long axon, which passes straight up into the molecular layer, where it bifurcates, forming two branches which run parallel with the surface in a direction at right angles to the plane of expansion of the dendrites of Purkinje's cells, apparently resting against the serrations on the edges of these processes. The second kind of cell in the granular layer is the so-called Golgi's cell—a large cell with many dendrites and an axon which terminates by frequent branches in the neighbouring grey matter.

FIG 296



Schema of constituent elements of cerebellum (modified from Böhm and Davidoff) On the left is a section of the cortex as it appears when stained by ordinary methods The middle portion represents diagrammatically a section at right angles to the laminæ, while to the right of the dotted line the section is taken in the same plane as the laminæ a, star-shaped cells of molecular layer, b, b, cells of Purkinje, c, 'Golgi cell', d, small cells of nuclear layer, e, 'tendril fibre', f, 'moss fibre'; g, axon of cell of Purkinje

The fibres making up the white matter are of three kinds—two afferent and one efferent. The *moss fibres*, so called from the curious thickenings they present in the nuclear layer, pass up into the grey matter and terminate by frequent branches in this layer. The *tendril fibres*, also afferent, end in a rich arborisation which surrounds the distal part of the cell and the bases of the dendrites of the cells of Purkinje. The efferent fibres are represented by the axons of the cells of Purkinje, which acquire a medullary sheath and run down into the white matter.

This slight sketch of the anatomy gives us a conception of the extreme complexity of choice presented to nervous impulses traversing the cerebellar cortex. Thus a discharge along an axon of the cell of Purkinje may be excited (1) by an impulse ascending the tendril fibres, or (2) by one ascending the moss fibres through the granule cells, and then passing by their bifurcating axon to the dendrites of the cells of Purkinje, or (3) by the star-shaped cells of the molecular layer and their basket-work round the body of Purkinje's cells.

Connections of the Cerebellum.—Although these have been already touched upon in dealing with the brain as a whole, they may be summarised here in order to guide us in the discussion of the cerebellar functions.

By the *inferior peduncles* afferent fibres pass to superior vermis—

1. From Clarke's column of the same side by the posterior cerebellar tract.

2. From both sets of dorsal nuclei, and therefore indirectly from the posterior columns and posterior spinal roots of both sides.

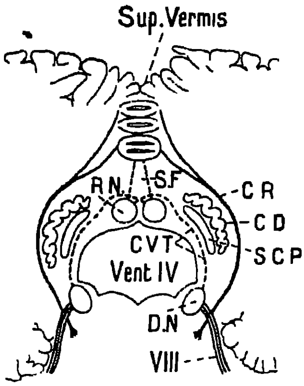
3. By the internal restiform body (C.V.T., Figs. 297 and 298) from the vestibular division of the eighth nerve, part of the fibres passing through Deiters' nucleus.

By the *middle peduncles* fibres pass to the other side of the pons, where they enter into relation with the frontal cortical and temporo-occipital fibres, which pass from the cerebral cortex of the opposite side by the lateral portions of the crusta to end in this region.

By the *superior peduncles* the dentate nucleus of the cerebellum, and to a certain extent the cortex, are connected with the red nucleus and thalamus of the opposite side. Moreover the fibres of the antero-lateral ascending tract enter the cerebellum by this peduncle and terminate in the superior vermis

It will be observed that, judging from the direction of degeneration, most of these tracts, so far as the cerebellum is concerned, are chiefly afferent. No direct connection of the cerebellum with the nuclei of motor nerves has been described, but there is a very important indirect connection by means of the so-called auditory nucleus or nucleus of Deiters. The connections of this nucleus are shown in Fig. 298. Receiving fibres from the roof-nuclei of the cerebellum, as well as directly from the semicircular canals by the vestibular nerve, it gives off a number of efferent fibres. These may be divided into two classes. One set, the vestibulo-spinal fibres, pass down the cord as the antero-lateral descending tract, the fibres of which terminate in the anterior cornu on the same side of the cord. The second set of fibres, passing inwards, terminate partly in the nucleus of the sixth nerve and partly turn upwards and downwards in the posterior longitudinal bundle, making connections with the nuclei of the fourth and third nerves, while the descending fibres run down in the anterior column and apparently end in the anterior cornu.

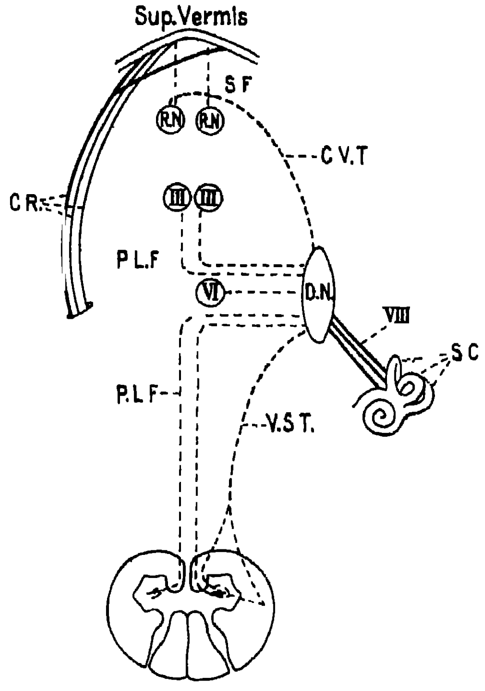
FIG. 297



Schematic representation of some of the connections of the cerebellum (Bruce) C R, inferior peduncle or restiform body, S C P., superior peduncle, C D, corpus dentatum, R.N, roof nuclei, S F, sagittal fibres from cortex to roof nuclei, C V T, cerebello-vestibular tract, D N, Deiters' nucleus, VIII, vestibular nerve

Functions of the Cerebellum.—We thus see that the cerebellum is connected directly with the sensory mechanisms chiefly of the same side of the body, with the cortex of the opposite cerebral hemisphere, and indirectly with the motor mechanisms of the same side of the body, as well as of the eye muscles. It is moreover specially connected with the semicircular canals. By its complexity and connections it is therefore eminently fitted to take its part in controlling and guiding all bodily movements, especially those of the same side of the body. It is therefore surprising to find how

FIG 298.



Schema of connections of Deiters' nucleus (Bruce) C R, restiform body, R N, roof nuclei, S F, sagittal fibres from cortex to roof nuclei, C V T, cerebello-vestibular tract, D N, Deiters' nucleus, III, VI, nuclei of third and sixth nerves, P L F, posterior longitudinal bundle, VIII, vestibular division of eighth nerve, S C, semicircular canals, V S T, vestibulo-spinal fibres

very slight relatively are the disturbances produced by its complete ablation. In fact we learn more from experiments in which only one half of the cerebellum has been removed, as we are then able to compare the affected with the relatively sound side. After such an operation there is at first marked loss of co-ordinating power. The animal tends to fall towards the side of the lesion, and we may get forced movements of the body or of the eyes to the opposite side. After some time these acute disturbances pass away, and the only point to be noticed is a loss of power and of tone in the muscles of the side of the body from which the cerebellum has been removed. Complete or extensive destruction of the cerebellum in man has a more evident effect, owing to the greater co-ordinating capacity necessary for maintaining the erect posture whilst standing and walking. In such cases we observe an inco-ordination of movement exactly resembling that of a drunken man, and this may at times be associated with nodding movements of the head or forced lateral movements (*nystagmus*) of the eyeballs.

It has been suggested that the chief action of the cerebellum is to exert a moderating restraining influence on the cortex cerebri. But the facts mentioned above seem to show that its action is rather to keep the motor mechanisms both of the cortex and the spinal cord in a state of wakefulness, ready to contract in co-ordinated sequence to peripheral stimuli.

More important is the connection of the cerebellum with the organs of static sense (the semicircular canals and the otolith organs in the saccule and utricle). We have seen that the spinal cord contains all the apparatus required for the carrying out of co-ordinated movements, with their complicated play of afferent and efferent impulses. Any such movement requires—

(1) The appropriate peripheral stimulus, usually applied to the skin, and, according to its character, exciting different sets of nerve fibres

(2) The centre or series of centres in the spinal cord. The afferent impulse on arrival at the cord causes discharge of motor impulses to certain muscles, and a central inhibition of the tone of the antagonistic muscles.

(3) The adaptation of the extent of the contraction to the original stimulus involves a secondary reflex, from muscle through cord; the afferent nerves of the muscle conveying to the centres accurate information as to the strength of contraction of the muscle.

A movement therefore is started by a skin impression involves reciprocal innervation (motor and inhibitory) of antagonistic muscles, and these responses are in their turn guided and controlled by afferent impulses excited by the movements and arising chiefly in the muscles themselves. If this apparatus is all in working order, why cannot an animal stand or walk (except with great attention and training) after the destruction of the cerebellum? The answer is to be found in the fact that every animal (quadruped or biped) is, when erect, in a state of unstable equilibrium, the slightest movement tending to displace the centre of gravity, so that the animal would fall if the displacement were not at once remedied by muscular contractions. It is the special office of the cerebellum to co-ordinate the movements (already co-ordinated with one another by the spinal cord) with the position of the body in relation to its centre of gravity. On this account it receives impulses from the semicircular canals, from the eyes, from skin, joints, and muscles, and sits, so to speak, on the motor path from cortex to spinal cord, maintaining continually a tonic hold on the muscles, which may be strengthened or relaxed according to the position of the animal.

The diagonal movements of the limbs in walking causes an alternate shifting of the centre of gravity to one side or the other. Each lateral movement would and does cause the animal to fall, if the position be not immediately remedied by the influence of the cerebellum.

After extirpation of the cerebellum in a dog, the animal falls to one side or the other as soon as it tries to walk. Later it learns to walk by an entirely new mode of progression, viz. a series of jumps, in which the hind limbs or fore limbs move together, being sprawled widely apart, so as to widen as much as possible the basis of support and avoid the alternate lateral displacements of the centre of gravity incident on the normal method of locomotion.

Emotional Expression

By appropriate stimuli it is possible to elicit in animals deprived of their cerebral hemispheres the outward bodily manifestations which we usually regard as the expressions of certain emotions Now an emotion is a psychical state, or state of consciousness, but it is dependent for its production on the existence of certain bodily changes—affections of the heart, vascular system, voluntary muscles—which are involuntary and reflexly produced. The mechanism for this reflex production is present in the lower cerebral centres, so that severe stimulation of a sensory nerve in a hemisphereless rabbit causes it to utter a long, plaintive scream. The brainless frog responds with a croak, almost indicative of pleasure, each time its back is gently stroked. In neither of these, nor in any similar cases, are we justified in speaking as if an emotional state of consciousness were present. We have no reason to think that the rabbit suffers pain, or that the frog is pleased, in the two above-mentioned experiments, but merely that certain changes in the bodily condition are reflexly produced, which, if the cerebral hemispheres were present, would be represented in consciousness as an emotion of pain or pleasure.

When a patient is slightly under the influence of chloroform, it frequently happens that all the emotional expressions are preserved, although consciousness is totally abolished; he may cry out or struggle when cut with the knife, and yet when he recovers from the anæsthetic he will state that he felt nothing whatever of the operation.

SECTION 4

CEREBRAL HEMISPHERES

Structure of the Cerebral Cortex

We have considered the connections of the hemispheres so fully in the previous sections that it remains now only to describe shortly the chief points in their structure.

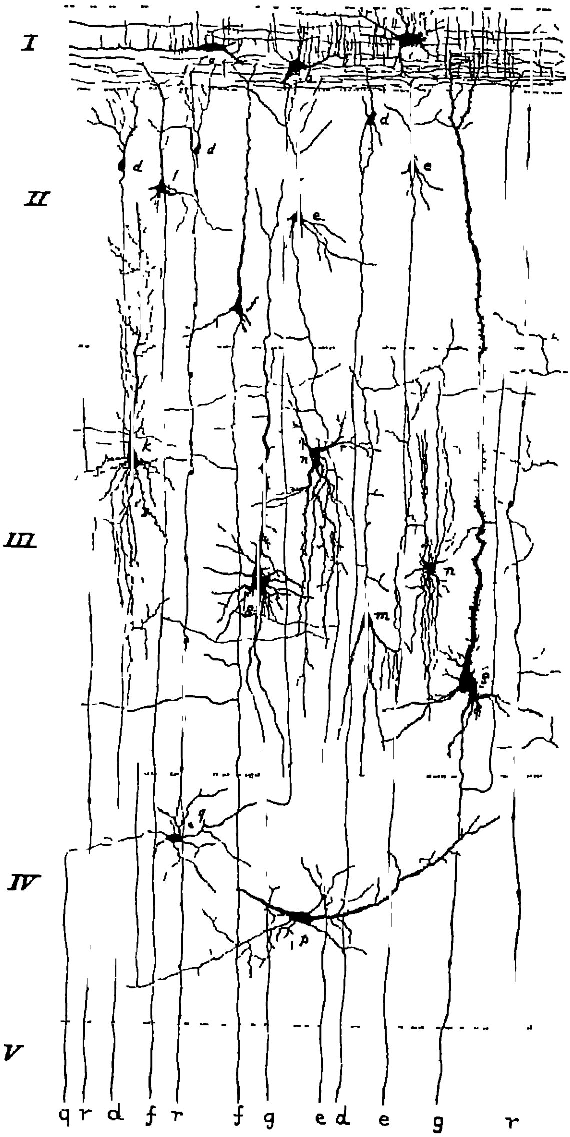
The cortex, as in the cerebellum, consists of a superficial layer of grey matter covering a central mass of white fibres, and, as in the cerebellum, increased area of surface with growing intelligence is afforded by the folding of the surface into convolutions and fissures. The chief convolutions are indicated in Figs. 301, 302.

On section the grey matter is seen to consist of many layers of nerve-cells embedded in a mass of tissue composed of neuroglia and many fine nerve-fibres, both medullated and non-medullated. The nerve-cells vary in size and shape, but one kind of cell is typical of this part of the nervous system. This is the pyramidal cell (Fig. 299, *g*), and consists of a cone-shaped cell-body with one large apical dendrite which runs towards the surface and breaks up in the superficial molecular layer into a number of branches. Dendrites also pass off from the sides and lower angles of the cell. The axon arising from the middle of the base of the cell passes downwards into the white matter, giving off collaterals in its course. Some of these, especially those from the large cells of the 'motor' area of the cortex, pass into the pyramidal tracts.

Although not so distinctly stratified as the cerebellar cortex, the cerebral grey matter can be divided into four (or in some situations five) layers. Most superficial is the molecular layer, composed of the dendrites of the pyramidal cells, and certain spindle-shaped '*pluripolar*' cells, *i.e.* cells with several apparently nervous processes running parallel to the surface. These are sometimes spoken of as 'association cells.'

Next to this comes a layer of small pyramidal cells, which is succeeded by a layer of small cells known as the *granular*

FIG 299

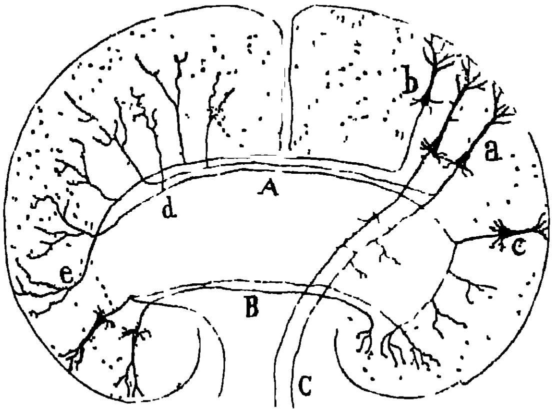


Diagrammatic section of cerebral cortex (from Barker, after Starr, Strong, and Leaming) I, molecular layer with *a*, bipolar cell, II, layer of small pyramidal cells, III, layer of large pyramidal cells , IV, polymorphous layer , V, white matter.

layer. Below this, in the motor cortex, is a layer of *large pyramidal* or *Betz* cells, while deepest of all is the '*polymorphous*' layer, composed of many types of cells, ordinary pyramidal cells, pyramidal cells with the base and axon turned towards the surface (cells of Martinotti), and 'Golgi cells' with a freely branching axon which terminates in the adjacent grey matter. Among the nerve-fibres passing between grey and white matter, four types (Fig. 300) can be distinguished:

a. Projection fibres, passing from the pyramidal cells to lower levels of the central nervous system. These include the various fibres, pyramidal and otherwise, that make up the internal capsule and the crusta.

FIG. 300.



Schematic section through cerebral hemispheres, to show chief classes of nerve tracts (after Ramón y Cajal) A, corpus callosum, B, anterior commissure, C, pyramidal tract; *a*, cell giving off projection fibre, *b*, cell giving off commissural fibre, *c*, cell with axon forming association fibres

b. Commissural fibres passing across the corpus callosum and anterior commissure to the opposite hemisphere.

c. Association fibres passing from one part of the cortex to another on the same side of the brain.

d. Afferent or sensory fibres, starting in most cases from the region of the thalamus and passing up to terminate by branching in the superficial layer of the cortex.

In a section through the cortex, stained by some method such as Weigert's, to display medullated nerve-fibres, in addition to the bundles of radial fibres running from the white matter perpendicularly to the surface, bands of tangential fibres are seen running parallel to the surface in certain situations, viz.:—

(*a*) A layer just under the surface of the cortex.

(*b*) A layer between the molecular and small pyramidal layer, the outer line of Baillarger.

(*c*) A layer between the granular and large pyramidal cell layers, the inner line of Baillarger.

(*d*) In addition to these a special layer of tangential fibres is present in the occipital lobe, running through the middle of the granular layer, and dividing it into two This is known as the line of Gennari

Differences are observed in the structure of various parts of the cortex corresponding to their functions Thus we may say roughly that the small pyramidal layer is chiefly associational in function, the large pyramidal cells are motor, the granular layer is sensory, while the polymorphous layer presides over the lowest cortical functions, such as the getting of food, the sexual instincts, etc.

Thus, in a low animal, such as the rabbit, the polymorphous layer has three times the thickness of the pyramidal layer, whereas in man, with his infinitely greater ideational powers, it is only one-third the thickness of this layer

In man, in an associational area such as the prefrontal convolutions, the pyramidal layer is almost as thick as all the rest put together. In the visual area (occipital lobes) the granular layer is the thickest, and is divided into two layers by the band of tangential fibres forming the line of Gennari In the motor area (chiefly the descending frontal convolution), we find below the granular layer, the well-marked large pyramidal cells, or Betz cells, though here also the pyramidal cell layer is very thick In this area the actual average thicknesses of the different layers are as follows —

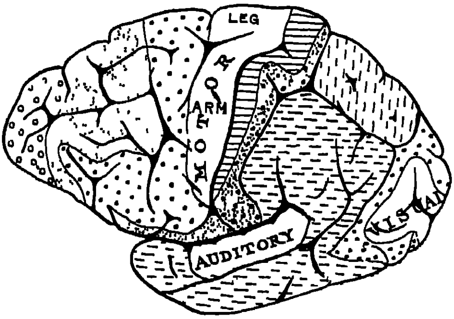
Molecular . .	0 34 mm.
Small pyramidal .	0 90 mm
Granular .	0 22 mm
Betz layer . .	0 22 mm
Polymorphous . . .	0 31 mm

Functions of the Cortex

We may come to some conclusions as to the general functions of the cerebral hemispheres if we compare the behaviour of a normal animal with one that has been deprived of its cerebral hemispheres. In the former case it is quite impossible to foretell what particular reaction may be evoked by any stimulus. It may produce the same effect as when applied to a brainless animal, but in most cases the reaction is modified in various ways. The animal is no longer a mere machine that can be played on at will, but is an individual whose actions are ruled by a guiding intelligence, who is actuated by motives and by feelings of fear, hunger, pain, and the like. In short, an animal, whose cerebral hemispheres are intact, presents phenomena analogous to those which in ourselves are associated with changes in the state of consciousness, and which we call volition or feeling.

It was formerly thought that in all their functions the cerebral hemispheres acted as an entity, and that any voluntary movement or any change in the state of consciousness might be considered as carried out by all parts of the hemispheres acting together. It has long been known however that each cerebral hemisphere innervates the opposite side of the body. Thus if the cortex of one hemisphere be destroyed or be functionally separated from the lower parts of the brain by destruction of the internal capsule, paralysis (hemiplegia) and loss of sensation on the opposite side of the body are produced. The paralysis is limited to voluntary, and may not affect reflex or emotional movements. It is interesting to note that those movements, which are usually carried out by the muscles on both sides of the body at the same time, are not so affected, probably in consequence of the close interdependence of the bulbar and spinal centres for these movements, and partly because these movements are equally represented in both hemispheres.

FIG. 301.

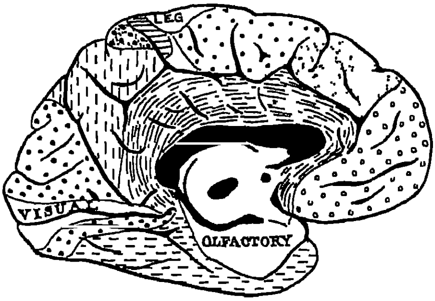


Motor centres on outer surface of monkey's brain.
(After Campbell and Sherrington)

Moreover, during the last twenty years, conclusive evidence has been brought forward of the localisation of function in the cerebral cortex of each side of the brain. This evidence is physiological and pathological, but in both cases it falls under the head of excitation, or of destruction and consequent paralysis. On exciting certain parts of the cortex, situated in the neighbourhood of the fissure of Rolando, definite co-ordinated movements of certain muscles or groups of muscles are produced, varying in their distribution according to the exact spot stimulated. Thus stimulation with the faradic or galvanic current of the convolutions at the upper part of the fissure of Rolando causes co-ordinated movements of the lower limb, of the middle part, movements of the upper limb; and of the lower part (including the third frontal convolution), movements of the head and face. In the higher apes and in man the motor centres all lie in front of the fissure of Rolando.

These experiments are corroborated by others in which definite parts of the Rolandic area of the cortex are destroyed.

Fig 302



Motor centres on mesial surface of monkey's brain (After Campbell and Sherrington)

Destruction of any given zone of the motor area produces paralysis of voluntary movement in the part represented by this portion of the cortex. Thus if, on stimulation of a spot near the centre of the fissure of Rolando, we obtain a definite movement of the arm of the opposite side, and we then excise the cortex at this spot, we find that after the operation the animal has lost voluntary power over this movement and over none other.

It was formerly thought that the grey matter was not directly excitable, and that the effects of electric stimuli were due to excitation of the underlying fibres of the corona radiata. The direct excitability of the grey matter is however proved by the following considerations.

1. There is greater 'lost-time' in the grey matter than in

the underlying white matter; that is, if we first stimulate the grey matter, and then shave this off and stimulate the white matter below, it is found that the latent period, which elapses between the time when the stimulus is sent in and the time at which the contraction takes place, is far greater in the former than in the latter case.

2. It is very common, as the result of excessive stimulation of the cortex, to get, not a single contraction of the group of muscles represented in the area stimulated, but an epileptic convulsion, which starts in this group of muscles and spreads thence to all the other muscles of the body. The convulsion consists of two stages:

(*a*) The tonic stage, in which all the muscles of the body may be in a state of continued contraction.

(*b*) The clonic stage, which lasts a good deal longer than the first stage, and consists of rapid rhythmical jerking movements of the muscles. This is followed by—

(*c*) A stage of exhaustion, in which the cortex is relatively inexcitable.

If the grey matter on both sides be removed, stimulation of the white fibres of the corona radiata does not produce a typical epileptic fit.

Pathological evidence bears out the results on localisation deduced from the physiological experiments just mentioned. Thus we have cases in which a tumour pressing on a part of the motor area causes twitching movements of the limb, or more or less complete epileptic convulsions, starting in the particular limb represented in the affected area of the cortex. On the other hand, cases frequently occur in which parts of the cortex are destroyed by pressure of a growing tumour, or by stoppage of the vessels supplying that area, giving rise to paralysis of definite muscles or groups of muscles.

After a movement has been abolished by extirpation of a definite area of the cortex, a considerable amount of recovery of movement may take place. The degree to which this may occur varies in different classes of animals, being more complete in the lower animals, such as the dog and rabbit, than in the monkey and man. It probably depends on the taking up of the functions of the extirpated area, partly by the adjoining regions of the cortex, and partly by the corresponding centre of the opposite hemisphere, all the centres of the two sides of the brain being functionally connected by means of the corpus callosum.

A point of considerable importance is the fact that movements rather than muscles are cortically represented. Thus stimulation of the right frontal lobes causes a movement (conjugate deviation) of both eyes to the left. In this movement the external rectus of the left side and the internal rectus of the right side are both set in action by stimulation of the right cortex. Similarly, we may produce movement of the head to the left by stimulation of the proper spot of the right cortex. In this movement the right sterno-mastoid and the left external oblique muscles are involved.

When we speak of motor centres it must not be supposed that motor impulses start *de novo* in the pyramidal cells of these centres. Here, as in all other parts of the central nervous system, the activity of the cells is excited exclusively by impulses arriving at them from other parts, and ultimately from the periphery of the body.

The absolute dependence of the activity of the pyramidal cells on afferent stimuli is well shown by an experiment carried out by Mott and Sherrington These observers divided all the posterior roots of the brachial plexus in the monkey, and found that the effect was to cause *motor* paralysis of all the finer movements of the arm and hand On exposing the corresponding area of the cortex and exciting it electrically, all the missing movements could be induced, showing that the cortical cells needed only the arrival of a stimulus to make them discharge No experiment could show better the ultimate reflex character of those movements which are generally distinguished as voluntary or purposive

These impulses, since they are afferent so far as the pyramidal cell is concerned, may be spoken of as sensory, and the collection of exalted reflex centres which make up the Rolandic area may therefore be justly termed *sensori-motor*. In fact, many observers believe that it is in the motor area that the sensation of touch and pressure on the corresponding limbs is perceived, and that the motor effect of exciting this part of the cortex is normally produced as a reaction to such touch or pressure sensations. Hence in extensive lesions of the motor area sensation as well as movement may be affected, and a certain amount of anæsthesia may accompany the paralysis.

Sensory areas.—If in the monkey the right occipital lobe be stimulated, there is movement of both eyes to the left.

This experiment by itself is capable of two interpretations: either the occipital lobe is to be regarded as a motor centre to the ocular muscles, or it is a sensory centre of sight, and the animal looks towards the left because visual sensations are aroused and referred to the left side of the field of vision. The latter explanation is shown to be true by the effects of extirpation. If the occipital cortex be destroyed, the animal is rendered blind on the side opposite the lesion. It is said to suffer from hemianopia (half-blindness). Excision of both the occipital lobes causes total blindness. Since the rays of the left half of the field of vision fall on the right-hand side of the two retinæ, and left hemianopia is produced by destruction of the right occipital lobe, the temporal half of the right retina and the nasal half of the left retina must be innervated from the right occipital cortex (Fig. 308). The connection, however, of the occipital lobe with the retina of the other side is more complete than with the retina of the same side, so that after destruction of the right lobe loss of vision is more extensive in the left than in the right eye.

FIG. 308

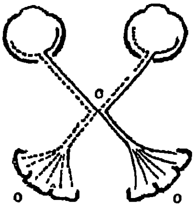


Diagram showing functional connection of occipital lobes with the two retinæ c. Optic chiasma o. Occipital lobes.

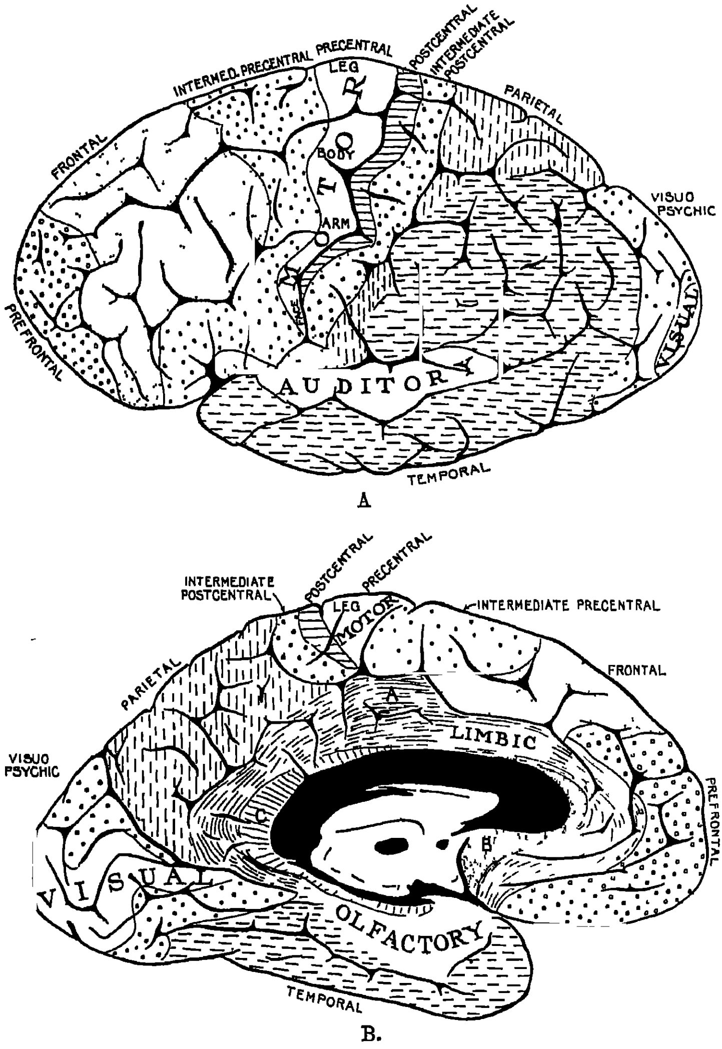
Our evidence as to the localisation of the other senses in the cortex is less complete. The sense of hearing is located by Ferrier in the superior temporo-sphenoidal lobe. Stimulation of this part causes pricking of the ears; destruction of it produces different effects according to the experimenter; it may give rise to deafness on the opposite side (Ferrier), or to no appreciable results (Schafer).

Clinical as well as anatomical observations however concur in locating auditory sensations in this convolution. The fact that after experimental extirpation the animal reacts to sounds does not prove the absence of impairment of auditory *sensa-*

tions, since the lower centres contain all the mechanism for a simple motor reaction to an incident sound-wave.

Smell and taste have been localised in the caput cornu Ammonis and the uncinate gyrus.

Fig. 304.



Human Brain showing outer (A) and mesial (B) surfaces, and the situation of the chief motor and sensory areas. The different shading represents the extent of each of these areas as determined by a study of the histological structure of the cortex. (Campbell.)

Many observers believe that general tactile sensibility as well as muscular sensibility is cortically represented in the same region as are muscular movements, *i.e.* in the Rolandic area.

From a study of the histological characters of the cerebral cortex, Campbell has concluded that the chief seat of tactile sensibility is to be found in the ascending parietal convolution, behind the fissure of Rolando.

In an animal such as the dog, we are able in this way to parcel out the greater part of the cerebral cortex into definite motor and sensory areas. It is possible to differentiate two grades of representation of sensation in the so-called sensory areas. The most primitive grade is concerned in the reception of afferent impressions from definite sense-organs and in the production of the appropriate cortical motor response. Surrounding or in immediate proximity to this area is generally found a wider area, which may give no effect on electrical stimulation, and is concerned in the 'working up' of the primitive sense-impressions into the more complex conditions, which we term ideas. The extent of these psychical areas increases relatively to that of the sensory areas as we ascend the animal scale. Thus in man the visuo-sensory area occupies but a small portion of the cortex and is concerned in the reception of simple visual sensations. Destruction of this area on one side causes half-blindness, or hemianopia. The greater part of the occipital lobe is taken up in the visuo-psychic area, the whole of which is engaged in the combination of sensations from the eyes, so as to form the visual ideas of things. Destruction of portions of this area will not necessarily affect sight, but may affect more or less the power of judging, through the medium of the eyes, of the nature of things seen. The relative extent of the different sensory and psycho-sensory areas of the human brain is represented in Fig. 304.

Aphasia.—If the cortex on the left side is destroyed, power of speech is totally lost. The same effect is produced if the lesion be limited to a small area in the third left frontal convolution (Broca's convolution). Our normal right-handedness is necessarily associated with and caused by the activities of the left hemisphere predominating over and guiding those of the right. In the movements that stand highest in the evolution of the cerebral functions, those of speech, the predominance of the left side is so marked that destruction of the association centre for lips and tongue on this side causes complete loss of the delicately co-ordinated movements by which speech is produced.

Besides this motor aphasia, which is brought about by a lesion of Broca's convolution, speech may be destroyed by injury of the sensory psychical centres (sensory aphasia). Thus in some cases in which the left superior temporo-sphenoidal lobe was involved, there has been a condition of word-deafness. The patient could not understand anything that was said to him. He might be able to talk volubly, but the words were mere gibberish, his auditory word-centre being absent, he was unable to appreciate the meaning of what he was saying, and so the motor processes went on unchecked by the criticism of sensory impressions. The talking of a

FIG. 305.

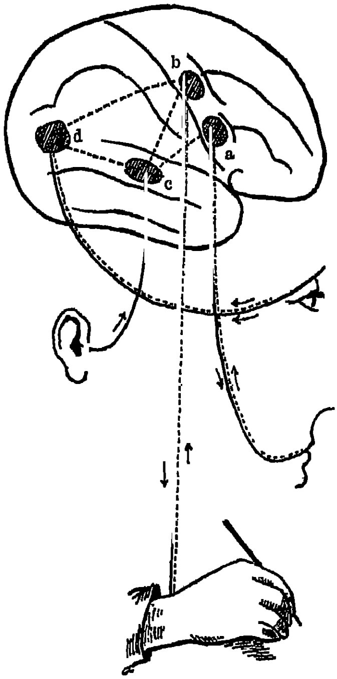


Diagram of cortical areas engaged in speech and writing (Ross) a Broca's convolution (motor lip and tongue area). b. Arm area c Auditory word-centre. d Visual word-centre man with word-deafness may be compared to the walking of a man with complete loss of muscular sense.

In the same way a lesion in the left occipital lobe may cause loss of power to read (alexia) from blotting out of all the higher visual memories, and more especially those connected with written and printed words.

Any of these lesions may be attended with inability to write, which in most people is intimately dependent on the auditory and motor speech memories. Most people in writing may be seen to move their lips slightly as they articulate the words to themselves, thus showing that in writing the arm-centre is acting in subordination to the mouth-speech centre in the third left frontal convolution.

Fig. 305 represents simply the relationships of the various centres on the left side to one another in speaking and writing.

The most striking change, as we ascend the scale of intelligence in animals, in the structure of the brain is the great development that occurs of brain-tissue, giving no response on stimulation and presenting no immediate connection either with motion or sensation. Such tissue is found in the pre-frontal and the parietal lobes, and in man forms the greater part of the cerebral cortex. The fibres of these lobes are found to acquire their myelin sheath a considerable time after birth, and continuous development may go on as late as the twentieth year. We are probably justified in ascribing to these association-centres the chief part in the functions of ideation and judgment. The ideas, which make up the greater part of our mental life and which determine our actions, cannot be regarded as essentially motor or sensory, though in them motor and sensory processes of the present are inextricably intermingled with the results of past sensory and motor impressions ; and there is a constant war of mutual excitations and inhibitions, the resultant of which is the behaviour of the individual.

SECTION 5

THE VASCULAR AND LYMPHATIC ARRANGEMENTS OF THE CENTRAL NERVOUS SYSTEM

The brain and spinal cord are enclosed in three membranes, the dura mater, the arachnoid membrane, and the pia mater.

The *dura mater* is a tough fibrous membrane, closely adherent in the skull to the cranial bones, of which it forms the periosteum, but in the spinal canal only loosely connected with the vertebræ.

The *pia mater* is a finely fibrillated connective tissue, closely adherent to the surface of both brain and spinal cord, and sending prolongations into all the fissures of these organs. It serves to convey the nutrient vessels to the nervous tissue.

The space between dura mater and pia mater is divided into two by a delicate membrane, the *arachnoid.* Both arachnoid and dura mater send processes along the issuing nerve-roots. The subdural and subarachnoid spaces are both lined with endothelial cells. Although anatomically separate, fluid can find its way with extreme ease from one space to the other, so that physiologically they may be regarded as if in communication. The subarachnoid space is put into connection with the ventricles of the brain and central canal of the cord by means of a small opening in the ependyma forming the roof of the fourth ventricle, which is known as the *foramen of Magendie.*

On incising the dura mater through the atlanto-occipital membrane, or in the spinal canal, a clear fluid wells up at the bottom of the wound, and a continuous flow of this fluid may with certain precautions be obtained by inserting a cannula into the subdural space in either of these situations. This liquid is the *cerebro-spinal fluid.* It consists of little more than a solution of the salts of the blood-plasma, and contains only the merest trace of proteid. This fluid appears to be formed in the ventricles of the brain by a process of secretion or transudation, modified by the cells of the ependyma covering the vascular fringes, which project into the ventricles from the velum interpositum and are known as the *choroid plexuses*. A slow formation of fluid is probably always going on. Any excess of fluid that is formed may either escape from the sheath of the dura mater along the issuing nerve-roots or, when the pressure of the fluid is higher than that in the venous sinuses, it may leave the cranial cavity by a direct filtration through the walls of these sinuses.

The lymphatic arrangements of the brain are still imperfectly understood. In the cortex cerebri the lymphatics are perivascular, *i.e.* form complete tubes round the blood capillaries. These perivascular lymphatics are said to be in communication with the subarachnoid cavity. If this is the case, the lymph must mix with the cerebro-spinal fluid; and it would seem difficult to account for the small percentage of proteid in this fluid—a percentage which seems quite inadequate for the nutritional needs of the nervous tissues.

The Intracranial Circulation

The brain is supplied with blood from the two vertebral and two internal carotid arteries, which anastomose at the base of the brain to form the circle of Willis. On account of this free anastomosis, one or two of these vessels can be obliterated without any effect on the circulation; and in the dog, all four arteries can be ligatured without producing more than a temporary lowering of the functions of the cortex cerebri. The cortex is supplied by the posterior cerebral from the basilar artery, and the middle and anterior cerebral arteries from the internal carotid. Although the area of distribution of these vessels does not coincide with the functional areas of the cortex, it is important to remember that blocking of the posterior cerebral artery will shut off the blood from the occipital lobe, so causing softening of this lobe and hemianopia; while blocking of the middle cerebral artery will affect the greater part of the Rolandic area, with widespread paralysis on the opposite side of the body, and probably some impairment of sensation, as its results. If the lesion be on the left side, complete aphasia will be produced. The symptoms of obstruction of the anterior cerebral artery will be less definite, since this vessel supplies only a small portion of the Rolandic area, together with the frontal lobes.

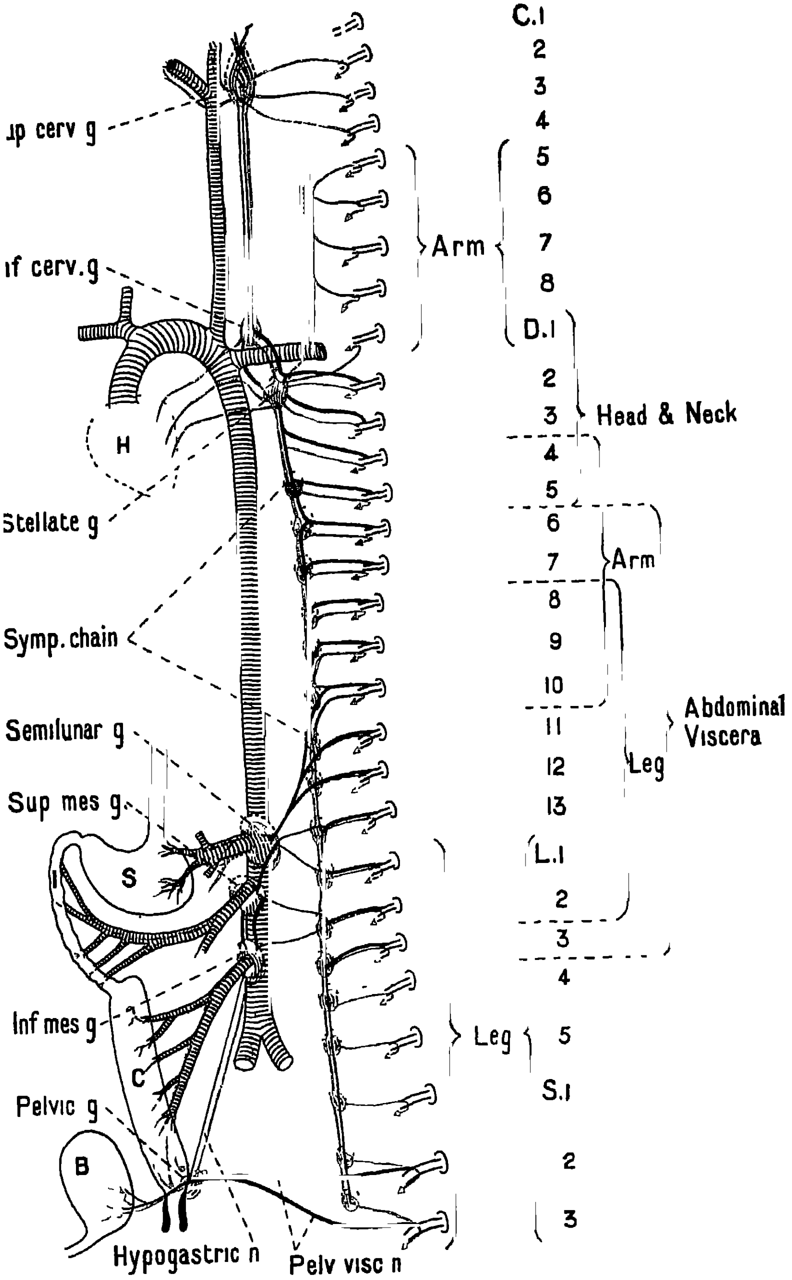
The optic thalamus and corpus striatum with the adjacent parts are supplied by small vessels which come off directly from the circle of Willis.

The veins of the brain pour their contents into a number of venous sinuses in the substance of the dura mater. The superior longitudinal sinus passes from before backwards along the vertex of the cranium at the top of the falx cerebri to the occiput, where it joins the straight sinus in the blood-cavity known as the torcular Herophili. The straight sinus carries the blood from the deeper parts of the brain, which have arrived at it by the veins of Galen along the velum interpositum. From the torcular the blood is carried by the lateral sinus on each side to the internal jugular veins.

The circulation in the brain differs from that in all other parts of the body, in that the cranial cavity forms a closed cavity with rigid walls. A small amount of space may be obtained in this cavity by the escape of cerebro-spinal fluid, but beyond this change, which can amount only to one or two c.c., we must say that the cubic contents of the cavity are invariable. Hence, the brain-substance being incompressible, dilatation of any one set of vessels can be obtained only at the expense of the constriction of another set of vessels. Thus a rise of arterial blood-pressure will cause a constriction of the veins until the pressure in these vessels rises to the pressure of the brain against them. Thus, as Leonard Hill has pointed out, with rise of arterial pressure the circulatory system of the brain tends to assimilate itself to a scheme of rigid tubes, and the whole energy of the arterial pressure is spent in maintaining an increased velocity of blood-flow.

The intracranial pressure is the same as the cerebral capillary and venous pressures. In the dog in the horizontal position it amounts to about 100 mm. H_2O, but it may vary according to the position and circulatory conditions of the animal within very wide limits without affecting the functions of the brain.

Although the cerebral vessels are supplied with nerve-fibres, we have as yet no definite experimental evidence of vaso-motor changes in these vessels. Since the vascular system of the whole body is under the control of a portion of the brain, viz. the vaso-motor centre, the circulation through the brain can be increased or diminished according to its supreme needs by alterations of the circulation in other parts of the body. Thus in the upright position, an adequate pressure is maintained in the cerebral arteries by constriction of vessels in the splanchnic area. The brain in fact uses this great vascular area as the means for regulating its own blood-supply.



Diagrammatic representation of the distribution of the sympathetic system The black lines represent the medullated preganglionic fibres, such as those making up the white rami communicantes, while the post-ganglionic fibres are printed in red On the extreme right of the figure is indicated the general distribution of the white rami arising from the several nerve-roots, while the double brackets point to the nerve-roots making up the limb plexuses. H, heart; S, stomach; I, small intestine, C, colon; B, bladder.

CHAPTER XVI

THE VISCERAL OR AUTONOMIC SYSTEM OF NERVES

We have already dealt with the chief functions of this system of nerves in connection with the various organs of the body. It remains only to consider some general points affecting the anatomy and functions of this system as a whole.

The visceral, autonomic, or splanchnic system of nerves includes the sympathetic system properly so called, and some of the cranial and sacral nerves.

The sympathetic system (Fig. 306) is composed of a chain of ganglia lying each side of the vertebral column, there being as a rule one ganglion to each spinal nerve-root. In the cervical region however these ganglia are condensed into two, the superior and inferior cervical ganglia, united by the cervical sympathetic trunk; and the upper three or four thoracic ganglia on each side are condensed to form the so-called stellate ganglion. At the bottom of the chain there is only one coccygeal ganglion for the coccygeal vertebræ.

In the abdomen is a second system of ganglia, in especial connection with the abdominal viscera, lying in front of the aorta and surrounding the origins of the large arteries to the alimentary canal. These are the semilunar or solar ganglia, the superior mesenteric and the inferior mesenteric ganglia.

Finally in the organs themselves we find a third system of ganglion cells either scattered or collected to form small ganglia. These are probably connected not only with the sympathetic but also with the other splanchnic nerves, cranial and sacral. The three systems of ganglia have been distinguished as the lateral, collateral, and terminal ganglia.

The ganglia of the sympathetic chain are connected with all the spinal nerves, just after they have given off their posterior division by means of the rami communicantes. These rami communicantes are of two kinds, white rami consisting

of small medullated fibres, and grey rami composed almost exclusively of non-medullated nerves.

It has been shown by Gaskell that the white rami are formed by fibres which have their origin in the spinal cord and perhaps in the posterior root ganglia; whereas the grey rami represent fibres which, arising in the sympathetic ganglia, run back to join the spinal nerves. The visceral outflow represented by the white rami is limited to a distinct region of the cord, viz. from the first thoracic to the third or fourth lumbar nerve-roots; whereas the grey rami pass from the sympathetic to all the spinal nerve-roots. It is found by experiment however that stimulation of a limited number of white rami produces all the effects that can be evoked by stimulation of the grey rami, showing that the impulses leaving the cord pass upwards and downwards in the sympathetic system and are broken somewhere in their course, being transferred to a fresh system which, by means of non-medullated nerves, carries them on to their destination.

The relationships of the white and grey rami are strikingly illustrated in the case of the pilomotor system of nerves. These in the cat arise from the cord by the anterior roots from the fourth thoracic to the third lumbar inclusive. Passing by the white rami to the sympathetic system, they travel upwards and downwards and end by arborisations in the various ganglia of the main chain. From the cells of each ganglion a fresh relay of fibres starts, which runs as a bundle of non-medullated nerves (the grey ramus) to the corresponding spinal nerve, with which it is distributed to its peripheral destination. The position of the cells in the nerve-path can be easily ascertained by the nicotine method described on p. 265. Each grey ramus causes erection of the hairs above one vertebra, whereas stimulation of one white ramus causes erection over three or four vertebræ, showing a distribution of the fibres of the white ramus to the cells in several successive ganglia.

We may summarise here the distribution of these pilomotor fibres in the cat.

1. For the head and upper part of the neck the fibres arise by the fourth to the seventh thoracic anterior roots, and have their cell-stations in the superior cervical ganglion. They travel as small medullated nerve-fibres from the white

rami up the sympathetic chain, through the stellate ganglion and ansa Vieussenii and up the cervical sympathetic.

2. The next set of nerve-fibres have their cell-station in the stellate ganglion. The white rami arise from the fifth to the eighth thoracic nerves, while the grey rami pass to the nerve-roots from the third cervical nerve to the fourth thoracic nerve.

3. The remaining nerves supplying all the rest of the body and tail arise by the white rami from the seventh thoracic to the third or fourth lumbar nerve, and are distributed as grey rami to all the spinal nerves below the fourth thoracic.

We thus see that, in speaking of the functions of a spinal nerve-root, we must clearly distinguish whether we mean the root as it rises from the spinal cord, in which case its visceral functions will include those of its white ramus, or whether we mean the made-up or complete spinal nerve after it has received its grey ramus (Fig. 307). In this latter case the visceral functions of the root will be more restricted than in the former case, and will have a different distribution. In stimulating the nerve-roots in the spinal canal it is sometimes possible, by weak stimuli, to display the functions of the corresponding white ramus, and then by increasing the stimulus to get superadded the effects due to excitation of the grey ramus in the made-up nerve, in consequence of the spread of current.

'When for example the eleventh thoracic anterior roots are stimulated in the spinal canal with weak shocks, a fairly long strip of hairs in the lumbar region will be erected, the maximum movement of the hairs being near the middle of the strip. This marks the area of distribution of the pilomotor nerves given by the eleventh thoracic nerve to the sympathetic. If then the strength of the shocks be increased to a certain point, the hairs in the long strip will of course be erected as before, but in addition there will be energetic erection of hairs in a short strip a little distance above the long strip, and separated from it by a quiescent region. This short strip is the same as that affected by stimulating the grey ramus or the dorsal cutaneous branch of the eleventh thoracic nerve. It marks the area of distribution of the pilomotor fibres received by the spinal nerve from the sympathetic' (Langley).

We may now indicate briefly the main course and functions of the fibres of the sympathetic system (Fig. 306):

1. The *head* and *neck* are supplied by fibres leaving the spinal cord by the first five dorsal nerves (chiefly by the

FIG. 807

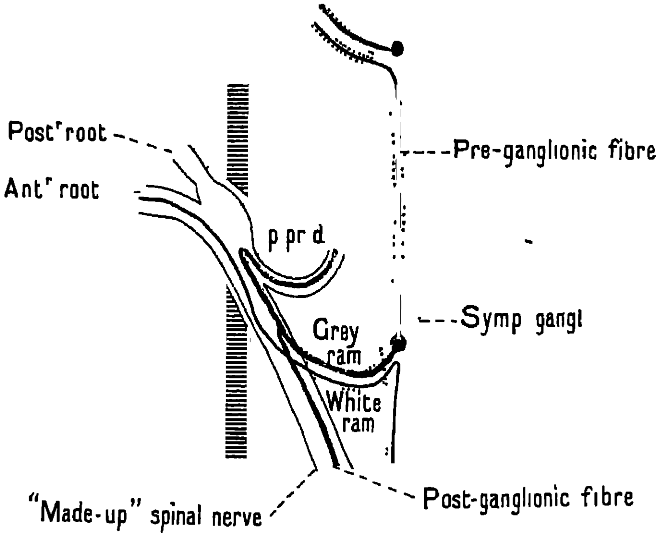


Diagram (after Langley) to show the manner in which a spinal nerve is completed by the entry of a grey ramus, containing fibres derived from cells in the sympathetic chain p pr d, posterior primary division (The post-ganglionic fibres are represented red)

second and third). They all have their cell-station in the superior cervical ganglion. They convey:

Vaso-constrictor impulses to the blood-vessels.
Dilator fibres to the pupil.
Secretory (trophic?) fibres to the salivary glands and sweat glands.
Vaso-dilator fibres to the lower lip (in the dog).

2. The *thoracic viscera* (heart and lungs) are supplied by the same five nerve-roots. The cell-station of these fibres is however situated in the stellate ganglion. They convey:

Accelerator or augmentor impulses to the heart.
Vaso-constrictor impulses to the pulmonary blood-vessels (?).

3. The *abdominal viscera* receive fibres from the lower six dorsal nerves and the upper three or four lumbar. Most of these fibres run through the sympathetic chain without making any connection with the ganglia, and have their cell-stations in the collateral ganglia of the solar plexus, the semilunar and superior mesenteric ganglia. On their way to these ganglia they form the greater and lesser splanchnic nerves. Their functions are:

Vaso-constrictor for stomach and small intestine, kidney, and spleen.
Probably vaso-dilator for the same viscera.
Inhibitory for both muscular coats of small intestine.
Motor for ileo-colic sphincter.
Secretory for pancreas (?).

4. The *pelvic viscera* are supplied by the lower dorsal and upper three or four lumbar nerve-roots. These fibres also pass by the main chain to make connections with the cells chiefly in the inferior mesenteric ganglia. They convey.

Vaso-constrictor impulses to pelvic viscera.
Inhibitory fibres to colon (both coats).
Motor and possibly also inhibitory fibres to bladder.
Motor fibres to retractor penis.
Motor fibres to uterus and vagina.

5. The *fore-limb* receives nerves from the white rami of the fourth to the tenth thoracic nerves. All these fibres are connected with cells in the stellate ganglion. They convey:

Vaso-constrictor impulses to blood-vessels.
Secretory nerves to the sweat-glands.

6. The *hind limb* is supplied by the nerve-roots from the eleventh thoracic to the third lumbar inclusive. The cell-stations of these fibres are situated in the sixth and seventh lumbar and first sacral ganglia. They convey:

Vaso-constrictor impulses.
Secretory nerves to the sweat-glands.

Every fibre of the sympathetic system is thus in some point of its course interrupted by a nerve-cell, and Langley has shown that this is the only cell-break in the fibre, *i.e.* every fibre is connected with one cell and one cell only. This law applies not only to the sympathetic fibres, but also to the fibres of the other visceral nerves. Each fibre therefore can be regarded as made up of two sections—a preganglionic fibre arising in the central nervous system and passing down to a ganglion as a fine medullated nerve-fibre, and a post-ganglionic fibre arising in this ganglion and continued generally as a non-medullated fibre to its peripheral distribution.

The efferent nerves of the sympathetic system arise in the cells of the lateral horn, and thus are homologous with the splanchnic fibres which arise in the medulla, viz. the motor root of the fifth, the facial nerve, and the motor root of the vago-glossopharyngeal.

According to Gaskell, the typical segmental nerve would have four roots: two somatic, the motor and sensory roots distributed to the skin and skeletal muscles, and two splanchnic roots, also motor and sensory, composed of small fibres and distributed to the viscera or structures which are visceral in origin, e.g. developed from branchial arches

In the spinal cord we have the proved separate origin of the motor fibres from the anterior horn and the visceral efferent fibres from the lateral horn; and a similar distinction may be made in the medulla between such somatic roots as the third, fourth, sixth, and twelfth nerves, and the splanchnic roots represented by the motor root of the fifth, the facial nerve, and the motor root of the vago-glossopharyngeal

In the medulla a distinction can be drawn between the central connections of the splanchnic afferent and the somatic afferent nerves Examples of the former are the vago-glossopharyngeal nucleus and the sensory nucleus of the fifth, and of the latter the long descending root of the fifth in connection with the substance of Rolando It is not known however whether a similar distinction can be drawn in the cord between the two sets of fibres.

Such of the visceral nerves as do not belong to the sympathetic system arise chiefly in the medulla and in the sacral region of the cord. Like those of sympathetic origin they all conform to Langley's law as to the possession of one and only one cell-station in their peripheral course. In most cases these cells lie near the periphery, and belong therefore to the terminal set of ganglia. The position of their nerve-cells is as follows:

Third nerve.—The branches to the iris and ciliary muscle are connected with cells in the ciliary ganglion.

Chorda tympani.—The vaso-dilator and secretory fibres of this nerve are connected with cells lying near the glands; those to the sublingual gland with cells in the sublingual ('submaxillary') ganglion; and those to the submaxillary gland with scattered cells lying in the hilum of the gland.

Vagus.—The inhibitory nerves to the heart are connected with ganglia in this organ itself. The motor fibres to the œsophagus and stomach have their cell-stations in the ganglion trunci vagi (in the alligator).

Pelvic visceral nerve.—This nerve is connected with a collection of ganglia lying in the hypogastric plexus at the base of the bladder. It has the following functions:

Dilator to vessels of the penis (hence its name of nervus erigens).

Dilator to vessels of pelvic viscera.

Motor to bladder, colon, and rectum.

Inhibitory to retractor penis.

It will be observed that in many cases the viscera get their nerve-supply from both sets of visceral nerves, and that in such cases the two sets of nerves are antagonistic in function. It is impossible however to draw a sharp line between the functions of the two sets, since the same nerve may be motor for one set of muscular fibres and inhibitory for another set in the same viscus. Thus the colonic branches of the inferior mesenteric ganglion are motor (constrictor) for the blood-vessels and inhibitory for the muscular walls of the colon.

Functions of the Sympathetic and Peripheral Ganglia

These ganglia consist of a mass of nerve-cells embedded in connective tissue, each cell being surrounded by a special capsule of endothelial cells. The nerve-cells, though in section resembling those in a posterior root ganglion, differ from these in being multipolar, each cell probably possessing one axon and several dendrites. The dendrites end in little arborisations round adjacent cells.

Since the main nervous system is characterised by the possession of nerve-cells, it was formerly thought that any collection of nerve-cells must partake of the co-ordinating and reflex functions of the central nervous system, *i.e.* must act as local nervous centres. All efforts have failed however to prove the existence of such a function, and we must conclude that the sole use of these ganglia is to serve as distributing centres. We may assume that one preganglionic fibre divides, and the branches arborise round several cells (Fig. 308), whence new fibres arise to carry the impulse to the periphery—an impulse in the case of which there is no need for any minute localisation. Indeed the essential part of a nerve-centre is not the nerve-cells at all, but the presence of a complex tangle of fibres, rendering possible the passage of impulses in all directions, the passage of an individual impulse however being limited by reason of the varying strength of the impulse, and the varying resistance of the many possible tracts. In many invertebrata the nervous system consists of a punctated material composed of a dense interlacement of fibrils, while the cells lie outside the centres, and have one thick process dipping into the nervous mass, from which process both axon and dendrites arise. In this case it has been found that extirpation of the cell-bodies does not destroy the capacity of the remaining fibrillated substance to act as a reflex centre.

Such a complex of fibres is found in mammals in the plexuses of Auerbach and Meissner which, as we have seen, act as local nerve-centres for the intestine. But all such mechanism is wanting in the sympathetic ganglia, which contain neither association fibres between different cells of a ganglion nor commissural fibres between the cells of adjacent

FIG 308

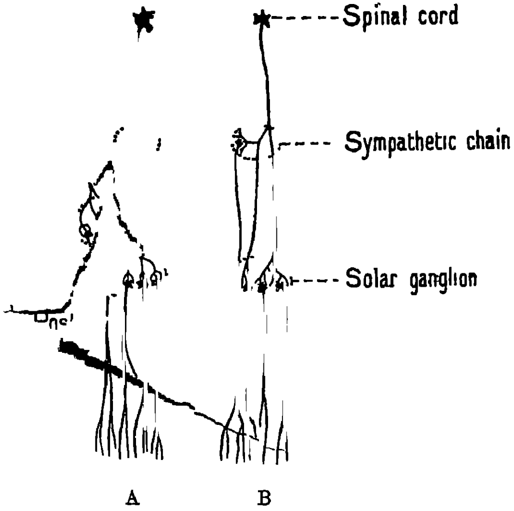


Figure (after Langley) to show the probable mode of connection of the fibres of the splanchnic nerve with nerve-cells A, usual type, all the fibres passing through the lateral chain to end in the collateral ganglia of the solar plexus, B, alternative condition, in which a small minority of the fibres have their cell-stations in the sympathetic chain The preganglionic fibres are black, the post-ganglionic red e p

se

ganglia. All the fibres in a sympathetic ganglion have either entered it from the white rami or are destined to leave it as fibres of grey rami.

Several reflexes formerly described in peripheral ganglia, as *e.g.* the 'submaxillary' ganglion, have been proved to be fallacious. There is however a certain group of phenomena which can be elicited in sympathetic ganglia, and which have been termed by Langley and Anderson pseudo-reflexes, or better, *axon reflexes*. If for instance we divide all the nerves going to the inferior mesenteric ganglion, leaving the bladder connected with the inferior mesenteric ganglion only by the hypogastric nerves, and then after dividing the left nerve stimulate its central end, we obtain a contraction of the right half of the bladder. This effect is abolished by painting the inferior mesenteric ganglion with nicotine, showing that the activity of the cells of this ganglion is involved in the process. It has been shown however by Langley and Anderson that this is not a true reflex, but is rather analogous to Kuhne's gracilis experiment (cf. p. 163). A preganglionic fibre arriving at the inferior mesenteric ganglion branches,

FIG 309.

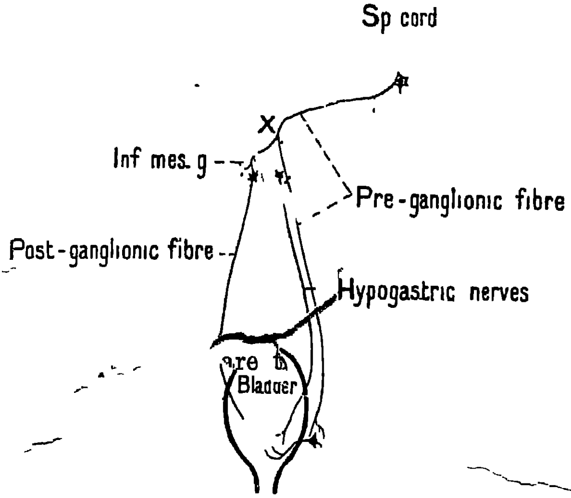


Diagram to illustrate Langley and Anderson's explanation of the hypogastric reflex as an axon reflex The division of the axon where the propagation or 'reflexion' takes place is at X one branch ending round the cells of the ganglion while the other branch passes down in the left hypogastric nerve to a cell situated near the base of the bladder (Fig. 309). When therefore we stimulate this nerve we are stimulating a preganglionic fibre, and the excitation spreads up to the point of junction of the two branches and then down the other branch to excite the cell in the inferior mesenteric ganglion. We thus obtain an apparent motor reflex by stimulation of a nerve which is itself motor.

Similar pseudo-reflexes can be obtained along the abdominal chain on the pilomotor nerves, but furnish no grounds for ascribing the property of reflex centres to peripheral ganglia.

CHAPTER XVII

REPRODUCTION

THROUGHOUT the animal kingdom we find the welfare of the individual subordinated to that of the species. The crowning act of an animal's life is the production of a new individual, fitted in all respects to take the place of the parent organism, and so to maintain the race on the earth. In the case of the lowliest unicellular organisms, which reproduce themselves only by fission, we cannot rightly speak of death from natural causes. One amœba divides into two new individuals similar to it in every way, and these in their turn divide again. Hence the amœbæ have with some right been spoken of as immortal. It is evident that any accommodation of the organism to its environment must, since it affects the whole cell, be transmitted in equal degree to the cells that are the offspring of the division of the parent. And so we may, in course of time, get a gradual change of type in the organism.

As we go higher in the scale we meet with more highly differentiated organisms, consisting of cell colonies, each member of which has its own appointed task to fulfil; and here we find that the office of reproduction also is confined to one cell or group of cells. The immortality of the amœba has been transmitted to this group of cells. From this point onwards, in the scale of animal life, we may regard the reproductive cells or germ-plasma as being continuous through successive generations. With the production of each new generation the germ-plasma divides into two parts: one part, the somatic half, forming what is generally understood as the individual, and being differentiated into various forms of cells to perform the multifarious functions of reaction associated with life; and the other half, persistent in its primitive form as the reproductive part of the individual, ready when the time comes to divide again and give birth to a new generation.

There are however many unicellular organisms in which the processes of reproduction are not quite so simple. These are able to multiply for a few generations by simple fission. At the end of this time, for the production of a new generation or series of generations, the conjoint action of two cells is required. In this process of *conjugation* two unicellular organisms come together and unite, their nuclei fusing to form one nucleus; the single cell thus made is capable of producing by fission several more generations. Here the cells that fuse are exactly alike in all respects. A little higher in the scale however, among the multicellular organisms, we find that the cells, which conjugate to form a new cell capable of developing into an individual, present somewhat different characters. The one cell, which has generally a certain amount of stored-up reserve material in its protoplasm, is the female element, and is called the ovum. The other cell, which is chiefly limited to the nuclear substance, is called the spermatozoon, and is the male element. This is the sexual mode of reproduction, which obtains in all the higher animals.

The conjugation of these two cells is not the union of the whole of two ordinary cells of two individuals. We find that both ovum and spermatozoon, before their union, undergo certain important changes, which have been more fully studied in the case of the former. The nucleus of the ovum just before fertilisation divides into two parts; one half is extruded with a small amount of the protoplasm, and the other remains in the main body of the ovum. The nucleus then undergoes division a second time, and again one half is extruded with a little protoplasm. The two extruded cells are spoken of as polar bodies, and do not undergo any further modification. The part of the nucleus left in the ovum is the female *pronucleus*. A similar change takes place in the male element, and the nuclei of the spermatozoa are equivalent to female pronuclei. These male and female pronuclei have the power of uniting together to form a whole nucleus, which is then capable of undergoing a long series of divisions to form a new individual. The union is effected by the penetration of the spermatozoon, which is in the higher animals mobile, into the ovum. Here for a while two nuclei are seen, the male and female pronuclei. They then fuse together, and the fertilised ovum is now potentially a new individual, partaking of the characteristics of both its parents.

Sexual life of man.—The period of active sexual life, during which the individual is capable of begetting or bearing children, begins in both sexes at the age of fourteen to sixteen, known as the age of puberty. In women, the beginning of this period is marked by the onset of menstruation. This is the occurrence of a flow of mucus and blood, which arises in the uterus, from the genital organs ; it lasts from three to five days, and recurs regularly every four weeks. Menstruation is associated with ovulation, which consists in the discharge of an ovum from the ovary. This latter contains follicles, each enclosing an ovum, which are known as the *Graafian follicles.* They are lined with a layer of cells—the *membrana granulosa*—which surround the ovum. In the course of development these cells proliferate and divide into two layers, each several cells thick, one of which lines the follicle, and the other—*discus proligerus*—encloses the ovum. The space between them is filled with colourless fluid, which contains proteids. This fluid gradually increases in amount until it forms a large projection on the surface of the ovary. At or just before each menstrual period a ripe Graafian follicle ruptures, and the ovum is discharged into the fimbriated extremity of the Fallopian tube, down which it is conducted to the uterus. This is accompanied with congestion of the genital organs, especially of the uterus, in consequence of which some of the smaller vessels of the uterine mucous membrane rupture, and give rise to the discharge of bloody fluid. The discharge of blood is accompanied with the fatty degeneration and disappearance of the most superficial parts of the mucous membrane itself.

When the Graafian follicle ruptures, hæmorrhage takes place into its interior. This is followed by a rapid proliferation of the cells of the membrana granulosa [illegible] new [illegible] grows in folds into the cavity, absorbing [illegible] of nine [illegible] forming the hæmoglobin int[illegible] development of the [illegible] takes place. This consists some [illegible]ks after dischar[illegible] the expuls[illegible] recognised [illegible] by muscular contractions of [illegible] uterus.

the *corpus luteum*. This is often spoken of as the *spurious* corpus luteum, to distinguish it from the corpus luteum of pregnancy. If pregnancy does not follow the discharge of the ovum, the corpus luteum disappears in from one to two months. If however pregnancy occurs, the corpus luteum becomes very large, forming a prominent projection on the surface of the ovary, and is to be seen almost to the end of pregnancy. Menstruation ceases during pregnancy, and is also generally absent during lactation. It ceases altogether between the ages of forty-five and fifty. After this time, which is known as the climacteric, the woman is no longer capable of bearing children.

Impregnation.—In animals which have a rutting season, ovulation is also accompanied by a flow of blood from the genital organs, and it is immediately after this period, which corresponds to the menstrual period, that impregnation is effected. In the human species impregnation may be effected at any time, and the union of spermatozoa with the ova may occur in the uterus, Fallopian tubes, or even in abnormal cases on the surface of the ovary.

If the ovum be not fertilised, it is cast out with the blood and products of disintegration of the uterine mucous membrane at each menstrual period. If however it be fertilised while in the Fallopian tube, a considerable thickening of the uterine mucous membrane takes place from proliferation of its cells, and it at the same time becomes very vascular. When the ovum reaches the uterus it becomes embedded in the mucous membrane covering the fundus of the uterus, which grows round and completely encloses it. This thickened mucous membrane, which is called the *decidua*, becomes fused with the outer layer of the ovum, and the latter, by means of its blood-vessels, derives its nourishment from the uterine mucous membrane.

At about the eighth week after impregnation the formation of the *placenta* takes place in the following manner:—A process of the internal hypoblastic layer of the embryo
spermat[illegible] out, carrying with it fœtal blood-vessels, and these
male pronu[illegible] their containing mesoblastic tissue extend to
nucleus, which [illegible] the embryo. This outgro[illegible] undergoing
divisions to [illegible] dua. At one spe[illegible] individual. The
penetra[illegible] villi, covere[illegible] the spermatozoon,

layer of cells and supplied with blood-vessels ; these project into maternal venous sinuses which have developed in the thickened mucous membrane of the uterus.

Through the medium of this placenta the developing animal obtains all the nutrient material it requires, both oxygen and combustible foodstuffs. The vessels of the fœtus are not in direct communication with those of the mother. The interchange of material between the two must be effected by the cells covering the placental villi, and takes place in fact through two layers of cells, the endothelium of the fœtal vessels and the epithelium of the villi. The placenta at the same time serves as an excretory organ for the fœtus, the effete material of the latter passing from the capillaries to the blood in the venous sinuses which bathe and surround the villi. The placenta is therefore alimentary, respiratory, and excretory.

FIG. 310

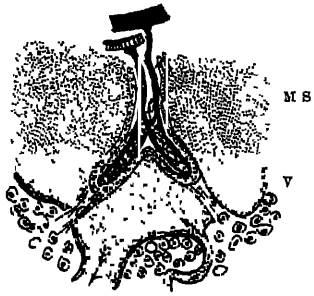


Diagram to show structure of human placenta M S Maternal venous sinus V Villus (outgrowth from chorion), containing artery and vein with capillaries derived from the umbilical vessels of the fœtus, and covered with a single layer of epithelial cells

Parturition.—While the ovum is undergoing its wonderful development, in which a complete human being is formed out of a single cell by division and differentiation, the uterus becomes very much enlarged, and its walls thickened by new growth of unstriated muscular tissue. At the end of nine months from the date of impregnation the development of the fœtus is complete, and parturition takes place. This consists in the expulsion of the fœtus by muscular contractions of the uterus.

Parturition or labour is divided into three stages. In the first stage the contractions of the uterus, which are painful and are hence spoken of as 'pains,' are devoted to dilating the os uteri. This is effected by contractions of the longitudinal muscles of the uterine wall, at the same time that the fœtus, contained in its bag of membranes, is forced against and expands the os.

When the os is fully dilated the uterine contractions change in character, becoming more prolonged, and are accompanied by strong contractions of the abdominal muscles, which force the child out through the vagina.

A short time after the birth of the child the pains recommence, and expel the placenta with the decidua and the fœtal membranes. In this third stage the connection of the uterine vessels with the placental sinuses is necessarily torn through. Bleeding however is prevented by the fact that the muscular fibres of the uterus remain firmly contracted after birth, compressing and obliterating the lumen of the torn vessels.

Directly the child is born, the uterus, contracting on the placenta, compresses its vessels and prevents a further supply of oxygen to the fœtal vessels. The child therefore becomes asphyxiated, and the venous blood, acting on the medullary centres, calls forth the first act of respiration, and the process is started which is to supply the needs of the new individual with oxygen for the rest of its life.

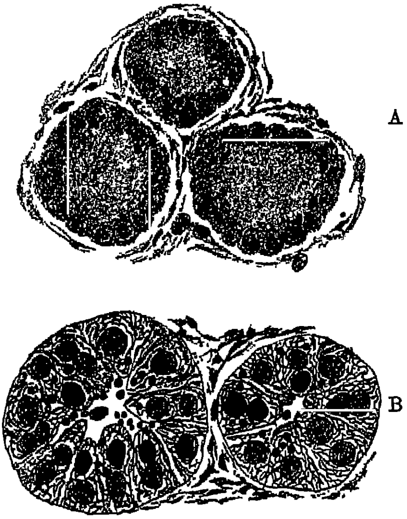
Parturition is obviously a complex reflex act, and depends for its normal carrying out on the integrity of the nervous connections of the uterus with the spinal cord. The centre for the act of parturition lies in the lumbar spinal cord, and it has been shown that parturition may go on normally in a bitch whose cord has been completely divided in the dorsal region. This act is then not necessarily dependent on the co-activity of the voluntary centres.

After birth the enlarged uterus rapidly diminishes in size in consequence of the atrophy and disintegration of the newly formed muscular tissues, and this *involution* is complete at the end of three months.

Lactation.—The young child at birth is not independent, but relies for many years for nourishment and protection on the parents. For the first nine to twelve months of the child's existence, under normal circumstances it is nourished entirely on the secretion of the mammary glands of the mother. The mammary glands vary largely in appearance according to the condition of the woman from whom they are taken. Before impregnation they are small, and on microscopical examination are seen to consist of a number of branching sinuous tubules, which are cut in various directions, and so give the appearance of a number of alveoli. These tubules are filled with a solid mass of epithelial cells. If impregnation occurs, a marked hypertrophy of the gland takes place, caused by the outgrowth of new columns of cells and the formation of new tubules from the pre-existing ones. At the same time the whole gland becomes more vascular from the enlargement of the blood-vessels in the interstitial connective tissue between the tubules. At the end of pregnancy the cells in the interior of the tubules undergo disintegration, leaving them lined with only a single layer of cells. The active secretion of milk begins shortly before or immediately after birth. The first milk that is secreted, which is called the *colostrum*, differs markedly from normal milk as already described (p. 508). It contains less casein and fat, but more albumen, than ordinary milk, and has in addition a certain amount of globulin. Owing to the large amount of these last two bodies, colostrum coagulates on boiling. Under the microscope, colostrum shows the presence of a number of cells with nuclei, or masses of protoplasm without nuclei (colostrum corpuscles). Some of these examined in fresh warm milk show amœboid movements. They probably have a twofold origin, from leucocytes which have wandered into the lumen of the gland, and from central cells of the tubules which have undergone disintegration. The active secretion of ordinary milk sets in on the second or third day after delivery. In the gland-cells we may distinguish a resting and an active condition, just as in the case of other glands. In the acini of a resting gland the lumen is wide and filled with milk, and the cells form a single flat nucleated layer at the periphery. The inner margins of some of the cells show jagged edges, and the protoplasm of all the cells contains a few small granules. In an active gland, on the other hand, the cells, which are long and columnar, project far into the lumen. Many have two nuclei, and the central parts of all the cells are filled with fat-granules and finer granules, which are probably protein in character (cf. Fig. 811).

The process which goes on in the transition from the resting to the discharged condition is as follows. In some of the cells, the central part, with its contained degenerated daughter nucleus, breaks away entirely from the basal part, and in the lumen undergoes rapid disintegration, furnishing to the fluid there protein, fat-globules, and probably sugar. The change in the cells however need not be so radical as this. Many simply discharge their fat-globules and their other contents into the lumen. This discharge of cell-contents is accompanied by a secretion of water and salts.

Fig 811



Sections of mammary gland of guinea-pig (fat-granules stained black with osmic acid)

A During rest

B During active secretion It will be noticed that in this case the active formation of products of cell-metabolism (granules, etc) begins with the commencement of secretion, and does not occur almost exclusively during rest, as in the salivary glands In the mammary gland, the active growth of protoplasm, the formation of granules from the protoplasm, and the discharge of these granules in the secretion, appear to go on at one and the same time

It must be remembered that in the secretion of milk its three chief constituents, caseinogen, lactose, and fat, are manufactured by the cells of the mammary glands out of the indifferent lymph which bathes them. This in its turn is replenished from the blood circulating through the gland. Caseinogen and milk-sugar are found nowhere else in the body, nor in any other animal secretion. The fact that the fat also is especially formed by the cells is shown by experiments, in which a bitch was fed on pure protein food, and excreted more fats in her milk than were contained in the whole of her food. An increase in the fat in the milk is said however to be brought about by an increased fatty diet, and abnormal fats given in the food may appear among the fats of the milk.

We see that the mammary gland in its mode of activity holds a position midway between the submaxillary mucous gland and the sebaceous glands of the skin. In the former the cells manufacture a substance—mucigen—out of materials brought to them by the blood, and this is discharged as mucin when occasion requires, part of the protoplasm of the cells always remaining intact, ready to build and store up mucigen in its meshes. In the sebaceous gland the secretion is furnished entirely by the disintegrated cells themselves, a continual new formation of cells going on at the periphery of the acini; the older cells, as they are forced towards the centre, undergo fatty degeneration, die, disintegrate, and are cast out as the fatty material known as *sebum* on the surface of the skin and at the roots of the hair

The further rearing of the child, its maintenance and education to fit it to become a useful member of society (that is, one fit to continue the race on the earth), are as much physiological necessities for the continuation of the species as the processes we have just been discussing. We are however here concerned with physiology in its narrower sense and need not carry it so far as the branch of this science known as sociology, the office of which it is to treat of these questions.

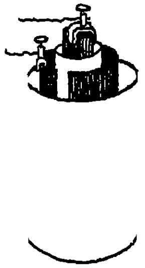
APPENDIX

A DESCRIPTION OF SOME ELECTRICAL INSTRUMENTS USED IN PHYSIOLOGY

The first requisite of the physiologist, if he desires to use electrical currents for excitation or any other purposes, is a source of a constant current. For this two forms of batteries are chiefly used, Daniell's and Grove's cells

A Daniell's cell (Fig. 312) consists of an outer pot containing a saturated solution of copper sulphate, in which is immersed a copper cylinder. To the cylinder at the top a binding screw is attached, by which the connection of the copper with a wire terminal is effected. Within the copper cylinder is a second pot of porous clay, filled with dilute sulphuric acid, in which is immersed a rod of amalgamated zinc. In this cell the zinc is the positive and the copper the negative *element*. Hence the current flows (in the cell) from zinc to copper, and if the binding screws of the two elements are connected by a wire, the current flows in the wire (outer circuit) from copper to zinc, thus completing the circuit. Since in the outer circuit the current flows from copper to zinc, the terminal attached to the copper is

Fig 312.



Daniell's cell.

called the positive *pole*, and that to the zinc the negative pole.

When the current is required to be very constant, the zinc may be immersed in a saturated solution of zinc sulphate instead of dilute sulphuric acid.

A Daniell's cell, though very constant, gives only a small current, owing to its small electromotive force and high internal resistance. When a stronger current is required, a Grove's cell (Fig. 313) may be used. In this cell the zinc is in the form of a cylinder, immersed in a cell containing dilute sulphuric acid. Within the cylinder is a porous pot filled with strong nitric acid, in which is immersed a sheet of platinum. In many cases the porous cell is made flat, and the zinc plate bent up round it, in order to decrease the distance between zinc and platinum, and so make the resistance as small as possible. In this cell the zinc is the positive and the platinum the negative plate; and so the terminal attached to the zinc is the negative, and that attached to the platinum the positive pole.

FIG. 313

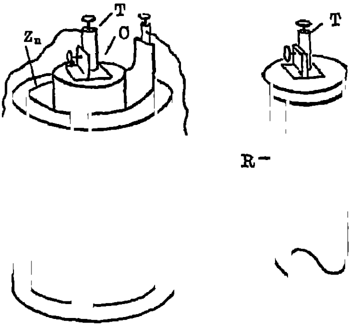
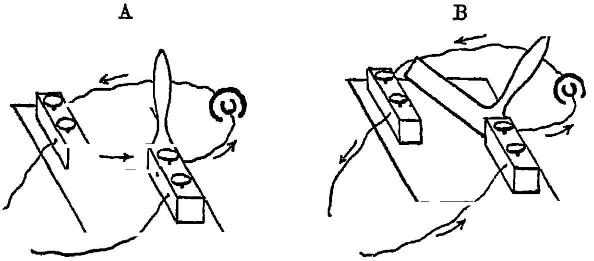


Diagram of Grove's cell. Zn Zinc cylinder O Inner porous cell T Terminal or binding screw of platinum. R. Sheet of platinum

Another very convenient form of battery, though not so constant as the two forms just described, is the *bichromate* battery, with a single fluid. This consists of a plate of zinc between two plates of carbon. The whole are arranged so that they can be immersed in or drawn out of the fluid at pleasure. The fluid used is a mixture of sulphuric acid and potassium bichromate. The wire attached to the carbons is the positive pole and the current in the outer circuit flows from carbon to zinc.

Various forms of keys and commutators are used for making and breaking a current, or for changing its direction. Of these the only ones that we need here describe are Du Bois Reymond's key, and Pohl's commutator or reverser. A Du Bois key consists of two pieces of brass, each of which has two binding screws for the attachment of wires. These are connected by a third piece, or bridge, which is jointed to one of the two side bits, so that it may be raised or lowered at pleasure (*v.* Fig. 314). It may be used either as a simple make-and-break key, or, as is more usual, as a short-circuiting key. In the first case one brass bank is attached to one terminal, the other to the other terminal. If the bridge be now lowered, the connection is made and the current passes. If the bridge be raised, the current is broken.

FIG 314.



Du Bois key, closed

Du Bois key, open

FIG. 314 A and B show the way in which the key is arranged for short-circuiting. It will be seen that four wires are attached to the key; two going to the battery, and two we may suppose going to a nerve. When the bridge is down, as in Fig. 314 A, the current from the cell on coming to the key has a choice of two routes. It may either go through the brass bridge, or through the other wires and nerve. The resistance of the nerve however is about 100,000 ohms, whereas that of the bridge is not the thousandth part of an ohm. When a current divides, the amount of current that goes along any branch is inversely proportional to the resistance. Here the resistance in the nerve-circuit is practically infinite compared with that in the brass bridge, and so all

the current goes through the bridge and none through the nerve. We say then that the current is *short-circuited.* If however the bridge be raised, as in Fig. 314 B, the only way the current can go is through the nerve, and so the whole of the current takes this course. This form of key is indispensable when exciting nerves with currents of high intensity. If an ordinary make-and-break key only be interposed in the circuit, excitation may occur even when the key is raised, the current having high enough potential to complete itself through the table and stand on which the preparation lies.

FIG 315.

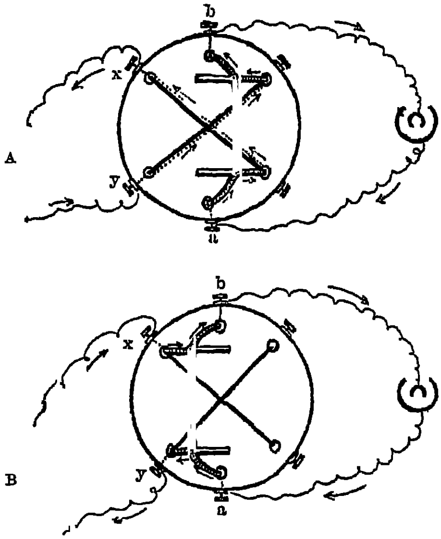


Diagram of Pohl's reverser

This is called *unipolar excitation,* and obviously cannot occur when the current is short-circuited.

Pohl's reverser is an arrangement for changing the direction of the current. It consists of a slab of ebonite or paraffin or other insulating material, in which are six small holes filled with mercury. A binding screw is in connection with the mercury in each of these holes. Two cross-wires (not in contact with one another) join two sets of pools together, as shown in Fig. 315.

A cradle consisting of two wires joined by an insulating handle carries two arcs of wire by which the pools at (a) and (b) may be put into connection with either (x) and (y), or the corresponding pools on the opposite side. It will be seen that with the cradle tipped to one side, as in Fig. 315 A, the current from the battery enters the reverser at (a) ; this proceeds up the wire of the cradle, down towards the right, then along the cross-wire to the pool at (x). (x) is therefore the anode, and (y) the kathode.

In Fig. 315 B the cradle has been swung over to the other side. Here the cross-wires are not used at all by the current, which passes from (a) up the sides and down the curved wire to (y). In this case (y) is now the anode and (x) the kathode, and the direction of the current through the circuit connected with (x) and (y) is reversed.

By taking out the cross-wires, Pohl's reverser may be used as a simple switch, by which the current may be led into two different circuits in turn.

The Induction Coil (Du Bois Reymond)

If a coil of wire in connection with a galvanometer be placed close to (but insulated from) another coil through which a current may be led from a battery, it is found that on make and break of the current of the second coil a momentary current is induced in the first. The induced current on make is in the reverse direction, that on break in the same direction as the primary current. The electromotive force of the induced current is proportional to the number of turns of wire in the coils. This principle is made use of in the construction of the induction apparatus. This consists of two coils, each containing many turns of wire. The smaller coil (R_1, Fig. 316), consisting of a few turns of comparatively thick wire, is the primary coil, and is put into connection with a battery. It has within it a core of soft iron wires, which has the effect of attracting the lines of force, concentrating them, and so increasing its power of inducing secondary currents. The secondary coil, R_2, of a large number of turns of very thin wire, is arranged so as to slide over the primary coil. It is provided with two terminals, which may be connected with the nerve or other tissue that we wish to stimulate. Since the electromotive force of the induced current is proportional to the number of turns of wire, it is evident that the electromotive force of the current delivered by the induction coil may be many thousand times that of the battery current flowing through the primary coil. The induced currents increase rapidly in strength as the coils are approached to one another ; the strength of these therefore may be regulated by shoving the secondary up to or away from the primary coil.

A short-circuiting key is always placed between the secondary coil and the nerve to be stimulated.

If only single induction shocks are to be used, a make-and-break key is put in the primary battery circuit, and the two wires from the battery and key are attached to the two top screws of the primary coil (*c* and *d*, Fig. 316). It is then found that the shock given by the induced current on break of the primary current is much stronger than that on make.

FIG 316

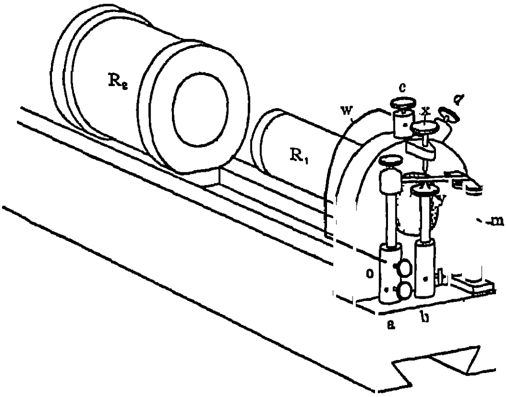
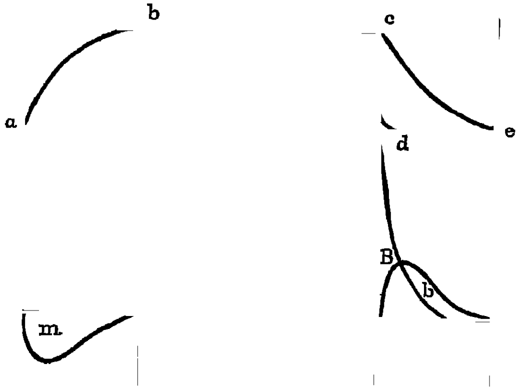


Diagram of inductorium R_1, primary ; R_2, secondary coil m. Electro-magnet of Wagner's hammer. w. Helmholtz' side wire

In endeavouring to explain this difference in the intensity of the make-and-break induction shocks, it must be remembered that the intensity of the momentary current induced in the secondary coil at make or break of the primary current is proportional (1) to the number of turns of wire in each coil, (2) inversely to the mean distance between the coils (i.e. the nearer the coils, the stronger the induced current); (3) to the *rate of change* in strength of the primary current. Now, when a current is made through the primary coil, induction takes place, not only between primary and secondary coils, but also between the individual turns of the primary coil itself. This current of self-induction, being opposed in direction to the battery current, hinders and delays the attainment by the latter of its full strength, and so slows the *rate of change* of current in the primary coil. Hence the intensity of the momentary current induced in the secondary coil is less than it would have been without the retarding effect of self-induction.

FIG 317



At break of the current, an extra current is also produced in the primary coil in the same direction as the battery current, and therefore tending to reduce the rate of change of the current from full strength to nothing. In this case however the primary circuit being broken, the current of self-induction cannot pass without jumping the great resistance offered by the air, so that its retarding effect on the rate of disappearance of the primary current may be practically disregarded. In Fig. 317 the line *a b c d* will represent the changes occurring in the primary current at make and break, *a b* corresponding to the make and *c d* to the break. The lower line represents the momentary currents induced in the secondary circuit, *m* being the current of low intensity and long duration produced by the make, and B the shock of high intensity and short duration caused by the sharp break of the primary current.

When we desire to use faradic stimulation—that is, secondary induced shocks rapidly repeated 50 to 100 times a second—we make use of the apparatus attached to the coil, known as Wagner's hammer (Figs. 316 and 318). In this case the wires from the battery are connected to the two lower screws (a and b, Fig. 316). Fig. 318 shows the direction of the current when Wagner's hammer is used. The current enters at (a), runs up the pillar and along the spring to the screw (x). Here it passes up through the screw, and through the primary coil (R_1). From the primary coil it passes up the small coil (m), and from this to the terminal (b) and back to the battery. But in this course the coil (m) is converted into an electro-magnet. The hammer (h) attached to the spring is attracted down, and so the spring is drawn away from the screw (x), and the current is therefore broken. The break of the current destroys the magnetic power of the coil, the spring jumps up again and once more makes circuit with the screw (x), only to be drawn down again directly this occurs. In this way the spring is kept vibrating, and the primary circuit is continually made and broken, with the production at each make-and-break of an induced current in the secondary coil.

FIG 318

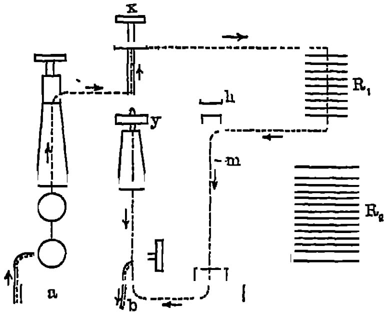


Diagram showing course of current in inductorium when Wagner's hammer is used

It is evident that, when the primary current is made and broken fifty times in the second, there will be a hundred momentary currents produced during the same period in the secondary coil. Every alternate one of these produced by the break of current in the primary will be much stronger than the intervening currents produced by the make. In order to equalise make-and-break induction-shocks, so that a regular series of momentary currents of nearly equal intensity may be produced, the arrangement known as Helmholtz's is used. In this arrangement the side wire (w), shown in Fig. 316, and diagrammatically in Fig. 319, is used to connect the binding screw (o) with the binding screw (c̣) at the top of the coil. The screw (x) is raised, so as not to touch the spring, and the lower screw (y) is moved up till it comes nearly in contact with the under surface of the spring. If we consider the direction of the current now, we

Fig. 319.

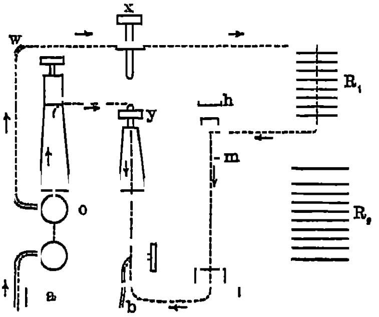


Diagram showing course of current when the Helmholtz side wire is used.

see that it enters as before at the terminal, travels up the Helmholtz's wire (w) to the screw (c), thence through the primary coil (R_1), then through the coil (m) of the Wagner's hammer, and so back to the battery. The coil (m), thus becoming an electro-magnet, draws down the hammer (h). In this act the under surface of the spring comes in contact with the screw (y). The current then has a choice of two ways. It may either go through the coil as before, or take a short cut from the terminal (a), up the pillar, along the spring, through the screw (y), and down to the terminal (b) back to the battery. As the resistance of this latter route is very small compared with the resistance of the primary coil, etc., the greater part of the current takes this way. The infinitesimal current which now passes through the coil of Wagner's arrangement is insufficient to magnetise this, and the hammer springs up again; thus the process is restarted, and the spring vibrates rhythmically. With this arrangement the primary current is never broken, but only short-circuited, and so diminished very largely. Hence the retarding influence of self-induction is as potent with break as with make of the current, and the effects on the secondary coil in the two cases are approximately equal. In Fig. 317 (c e) represents the change in the primary current when the current is short-circuited instead of being broken, and (b) represents the effect produced in the secondary coil. It will be seen that the currents (m) and (b) are practically identical in intensity and duration.

FIG 320.

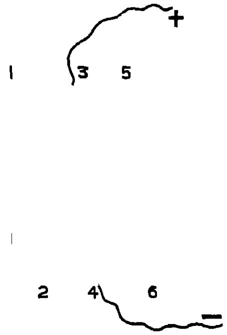


Diagram to show the mode of construction of a condenser

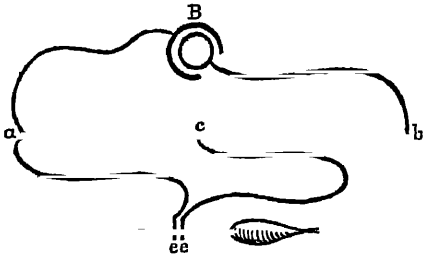
Condenser.—If two plates of metal separated from one another by a thin insulating layer of dielectric such as air, glass, mica, or paraffined paper, be connected with the two poles of a galvanometer, each plate acquires the potential of the pole of the battery with which it is connected, and receives therefrom a charge of electricity (positive or negative). If the connections be broken the two plates retain their charge. If now they be connected by a wire they discharge through the wire, and if a nerve be inserted in the course of the wire, it may be excited by the discharge.

The amount of electricity that may be stored up in this way will depend on the extent of the plates and their proximity to one another, as well as on the E.M.F. of the charging battery. In order to get great extent of surface, a condenser is built up as in the diagram (Fig. 320) of a very large number of plates of tinfoil, separated by discs of mica or paraffined paper. Alternate discs are connected together: thus 1, 3, 5 are connected to one pole, while 2, 4, 6 are connected to the other.

The *rheocord* is used to modify the amount or strength of current flowing through a preparation. One form of it is represented in Fig. 321. A constant source of current at B causes a flow of electricity from *a* to *b* through a straight way. As the resistance of this wire is the same throughout its length, the fall of potential from *a* to *b* must be constant.

The nerve, or whatever preparation that is used, is connected with the straight wire at two points, at *a* and at *c*, by means of a sliding contact or rider. Supposing that there is an electromotive difference of one volt between *a* and *b*, it is evident that if *c* is pushed close to *b*, the E.M.F. acting on the nerve will be also one volt. The E.M.F. however may be made as small as we like by sliding *c* nearer to *a*. Thus if *a b* is one metre, and there is a difference of one volt between the two ends, then if *c* be one centimetre from *a*, the E.M.F. acting on the nerve will be $\frac{1}{100}$ volt. Thus we alter the current passing through the nerve by altering the E.M.F. which drives the current.

Fig 321



The *galvanometer* is an instrument used to measure strength of current. Its construction depends on the fact that, if a small compass be suspended within a coil of wire and a current be passed through the wire, the compass is deflected, and tends to take up a position at right angles to its former one. In practice a pair of such magnetic needles are usually employed, arranged reversely, as in Fig. 322, where *a* and *n* represent the north-seeking ends of the magnets *a b* and *s n*. On arranging them in this way the effect of the earth's magnetism on them is weakened or annulled, and they are spoken of as *astatic*. A bar compass is suspended over the galvanometer, by the adjustment of which the force with which the suspended pair of magnets tends to 'set' in one direction may be increased or diminished. In Thomson's galvanometer, as it is used for nerve work, the coils of wire have a resistance of 5,000 to 20,000 ohms. Between the two magnets is fixed a small mirror. The swing of the magnet is recorded by observing the excursion of a spot of light reflected by this mirror on to a horizontal graduated scale.

FIG 322

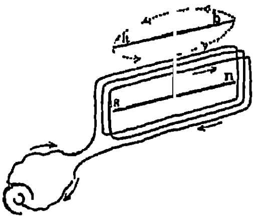


Diagram of galvanometer, with astatic pair of magnets The arrows show direction of current from battery, and the swing of the needles

In thermo-electric experiments, when very small differences of potential have to be measured through a small resistance, the galvanometer must also have a small resistance, which here should not be more than one ohm.

The *capillary electrometer* is an instrument for recording and measuring difference of potential. That is to say, if connected with two points, it measures the force which would make a current flow between these two points if they were connected with a wire.

Its structure is very simple. It consists of a glass tube drawn out to a fine capillary point. This tube with the capillary is filled with mercury. The point dips into a wide tube containing dilute sulphuric acid, at the bottom of which is a little mercury. Two platinum wires melted into the glass and dipping into the mercury serve as terminals. In consequence of capillary attraction the acid ascends some way into the capillary tube, and the force of this can, with fine capillaries, sustain the weight of several inches of mercury.

When the instrument is used, the meniscus of the mercury in the capillary at its junction with the acid is observed under the microscope, or a magnified image of it is thrown on a screen with the aid of the lime or electric light.

FIG 323

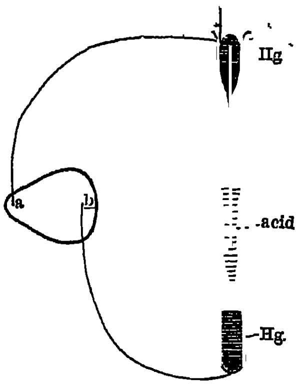


Diagram of capillary electrometer Hg, Mercury The two terminals are represented as leading off two points at the base and apex of a frog's heart, a b

If now the capillary and acid be connected with two points, it will be observed that any difference in the potential of these two points causes a movement of the meniscus If the point connected to acid be negative as compared with the point connected to mercury in capillary, the meniscus moves towards the point of the capillary. If the acid be positive as compared with the capillary, the meniscus moves away from the point. It is further found that the extent of the excursion is proportional to the difference of potential.

Since the capillary electrometer appears to have no latent period, and is free from instrumental vibrations, it is extremely useful in recording the quick changes in potential occurring in the diphasic electrical changes that accompany every contraction-wave in the body.

The excursions lend themselves well to photography, so that we may obtain a graphic record of every electrical variation, and thus determine its extent and its time-relations.

It must be remembered that this instrument is an electrometer (measurer of difference of potential), and not a galvanometer (current-measurer). When the electrometer is connected with two points at different potential, no current passes through it. Hence the use of non-polarisable electrodes is not so essential in experiments with this instrument as when we make use of the galvanometer.

2616
L:3
L07

[illegible] R.C. and the result of their disintegra[illegible] [illegible] the process. [illegible]

[illegible]

[illegible] of WBCs and [illegible] [illegible] the total no. of W.B.C. [illegible] calculated. [illegible]

[illegible] P. 3 [illegible]).

[illegible] and vital [illegible]

[illegible] in vitro [illegible] of clotting of blood [illegible]

INDEX

Absorption of foodstuffs, 349–359
  of lymph, 295
Accelerator nerves, 250
Accommodation, 552
Adaptation, visual, 566
Adrenaline, 252, 520
Aerotonometer, 492
Air, changes of composition in respired, 386
Alanine, 32
Albuminoids, 46
Albumens, 39
  derived, 40
Albumoses, properties of, 41
Alimentary canal, 8
Alveolar air, 388
Amboceptor, 85
Amino-acids, 33, 333, 487
Ammonia, excretion of, 438, 450
  formation of, 139
Amœboid movement, 157
Amyloid substance, 46
Amylopsin, 331
Anabolic nerves, 271
Anabolism, 4
Anacrotic pulse, 229
Anæmia, 285
Anæsthetics, action on nerve, 180
Anelectrotonus, 169
Antibody, 85
'Antipeptone,' 333
Apex-beat, 219
Aphasia, 663
Apnœa, 417
Arginine, 36
Arteries, extensibility of, 190
  peripheral reactions of, 278
  pressure in, 192
  structure of, 189
Arteries, velocity in, 201
Aspartic acid, 34
Asphyxia, 404
  influence on blood-pressure, 275
Assimilation, 4, 7, 26
Astigmatism, 560
Auditory sense, 544–549
Auerbach's plexus, 370
Auto-oxidisable substances, 28
Axon, 588

Basophile corpuscles, 61
Batteries, 694
Bidder's ganglia, 235
Bile, 338–346, 353
  pigments, 343
    source of, 69
  salts, 341
Bilirubin, 343
Biliverdin, 343
Bladder, movements of, 469
Blood, 57–86
  coagulation of, 75–84
  composition of, 84
  gases of, 391
  reaction of, 84
  specific gravity of, 84
  total quantity of, 283
  velocity of, 201
Blood-corpuscles, 58–74
  chemistry of, 62–67
  estimation of, 73
  formation of, 70
  life history of, 68
Blood-plasma, conditions of clotting, 83
Blood-platelets, 61, 83
Blood-pressure, 192
  effect of asphyxia on, 275
  in heart, 215, 227

Blood-pressure, respiratory undulations of, 423
Blood-serum, 75
  poisonous effects of, 285
Blood-vessels, innervation of, 260
  reflex alterations of, 271
  structure and properties of, 189
  velocity of blood flow in, 201
Brain, circulation in, 667
  connecting tracts in, 626
  functions of, 22, 642–652
  localisation in, 656–663
  membranes of, 666
  structure of, 612–638
Bronchi, innervation of, 418

CALORIMETER, 501
Cane-sugar, 54
Capillaries, circulation in, 280
  permeability of, 290
  velocity in, 204
Capillary electrometer, 125, 705
Carbohydrates, absorption of, 354
  chemistry of, 51–56
  metabolism of, 489–496
  of milk, 509
Carbon dioxide in blood, 391
    influence on respiratory centre, 405
  monoxide, 400, 420
Carboxyhæmoglobin, 64
Cardiograph, 220
Cardiometer, 255
Caseinogen, 44, 323, 508, 693
Cells, oxidative changes in, 28
  processes of reduction in, 28
Cellulose, 56
Centre, cardio-inhibitory, 251
  respiratory, 402
  vaso-motor, 260
Cerebellum, 645–651
Cerebral circulation, 667
  hemispheres, 653–665
Cerebro-spinal fluid, 666
Cerebrum, 22, 653
'Characteristic,' 101
Chemical constituents of the body, 25 *et seq.*
Cholesterin, 49, 343
Choletelin, 343
Chondrin, 46
Chondro-proteins, 46
Ciliary movement, 157
Circulation, 189–285
  capillary, 280
  course of, 11
  influence of gravity on, 278
  in lungs, 422
Circulation-time, 205
Coagulation, intravascular, 82
  of blood, 75
  of colloids, 31
  of milk, 324
  of muscle-plasma, 131
Coagulin, 86
Cold spots, 528
Colloids, 31
Colour vision, 572
Commutator, 696
Compensation in heart, 257
Complement, 85
Condenser, use of, 175, 703
Conduction in nerve, 169
Cones, 562, 567
Contractile tissues, 87–158
Contraction, isometric, 107
  isotonic, 107
  law of, 171
  of heart muscle, 2
  of muscle, 102
  paradoxical, 186
  propagation of, in heart, 237
  wave, 108
Contrast phenomena, 575
Co-ordination, 15
Cortex, functions of, 656
  structure of, 653
Cranial nerves, 634
Creatine, 36, 133, 441
Creatinine, 449
Crystallin, 40
Curare, action of, 95
Cutaneous sense, 526
Cystine, 36, 333
Cytase, 56

DEFÆCATION, 375
Degeneration, 584
  retrograde, 592
Deglutition, 368
Demarcation current, 121, 127
Depressor nerve, 272
Dextrin, 56
Dextrose, tests for, 53

Diabetes, 490
Diabetic coma, 495
Diamino-acids, 35, 333
Diaphragm, movements of, 379
Dicrotic wave, 226, 230
Diet, 507
Digestion, mechanisms of, 298–376
  muscular mechanisms of, 368–376
Diphthongs, 432
Di-saccharides, 54
Dissimilation, 4
Ductless glands, 513–521
Dys-oxidisable substances, 28

EAR, structure of, 544
Elastin, 47
Electrical changes in glands, 312
    in muscle, 120
    in nerve, 164
  organs, 128
Electrodes, 98
  non-polarisable, 120
Electrotonic current, 182
Electrotonus, 167
Emotional expression, 651
End-plates, 92
Energy of nerve-stimuli, 175
Enterokinase, 331, 347
Eosinophile, 60
Equilibrium, maintenance of, 643
Erepsin, 304, 347
Excitation of muscle, 95
Excretion, 12, 375, 434
Eye, accommodation in, 552
  adaptation of, 566
  chromatic aberration of, 558
  movements of, 563, 635
  refractive media of, 552
Eye-ball, nutrition of, 580

FÆCES, composition of, 361
Fat, formation of, 485
Fatigue in nerve, 177, 188
  of muscle, 141
Fats, absorption of, 350
  chemistry of, 48–50
  emulsification of, 336
  of milk, 509
Ferments, 299–304
Fibrin, 75
  precursors of, 78
Fibrin ferment, 80
Fibrinogen, 79
  tissue-, 82
Foodstuffs, fate in organism, 478–512
  heat-equivalents of, 482

GALACTOSE, 54
Galvanometer, 704
Ganglia, reflex action in, 683
Ganglion cells, functions of, 680
Gases, irrespirable, 421
  of blood, 391
  respiratory interchange of, 386–401
Gastric juice, 316
Gelatin, 46
  influence of pancreatic juice on, 335
Glands, *see also* Secretion
  ductless, 513–521
  salivary, 307
  sebaceous, 473
  sweat-, 474
Glaucoma, 581
Globin, 65
Globulins, 39
Glucosamine, 45
Glucose, 53
Glutamic acid, 36
Glycine, 34
Glycocholic acid, 342
Glycogen, 56, 489
  in muscle, 133
Glyco-proteins, 44
Gycosuria, 492
Glycuronic acid, 45, 492
Gracilis experiment, 164
Gustatory sense, 539

HÆMATIN, 65
Hæmatogen, 72
Hæmatoidin, 67
Hæmatolysis, 68
Hæmatoporphyrin, 67
Hæmin, 65
Hæmochromogen, 66
Hæmocytometer, 73
Hæmodromograph, 202
Hæmodromometer, 202
Hæmoglobin, 58
  compounds with gases, 62
  crystallisation of, 62

Hæmoglobin, destruction of, 68
  estimation of, 74
  fate of, 345
  formation of, 69
  spectrum of, 66
Hæmoglobinometer, 74
Hæmolysis, 85, 285
Hæmorrhage, effects of, 285
Hæmotachometer, 203
Hearing, 544–549
Heart, action of asphyxia on, 275
  afferent nerves of, 250
  anatomy of, 206
  automatic power of, 235
  compensation in, 257
  frog's, anatomy of, 234
  influence of drugs on, 251
  mammalian, innervation of, 245
    rhythm of, 242
  negative pressure in, 218
  output of, 253
  pressure in, 215, 226
  rhythm of, 233
  work of, 253
Heart-beat, phenomena of, 210
Heart-impulse, 219
Heart-muscle, properties of, 236
Heart-sounds, 218
  record of, 221
Heart-valves, action of, 211
Heat, production of, 501
Heat-formation in nerve, 165
  in muscle, 114
Heat-spots, 528
Hemianopia, 661
Hexone bases, 33, 334
Hexose, 51
Hippuric acid, 449
Histidine, 36
Histones, 37, 42
Hydrobilirubin, 453
Hypermetropia, 560

IMPREGNATION, 688
Induction coil, 698
Inflammation, 280
Inhibition, 607
  effect of strychnine on, 607
  of involuntary muscle, 156
Inogen, 138
Inosit, 133
Intestinal juice, 347
Intestine, large, innervation of, 374
  movements of, 374
  structure of, 349
Intraocular pressure, 580
Invertin, 304, 347
Iris, movements of, 556
Irritability, 2
  specific, 164
Islets of Langerhans, 329, 495
Isometric contraction, 107
Isotonic contraction, 107

KATABOLIC nerves, 271
Katabolism, 4
Katacrotic pulse, 229
Katalytic phenomena, 29
Katelectrotonus, 169
Keratin, 47
'Kernleiter,' 183
Keys, 699
Kidneys, functions of, 434–466
  innervation of, 464
  metabolic functions of, 466
  structure of, 454
  work of, 464
Knee-jerk, 609

LACTASE, 332
Lactation, 690
Lactic acid, 55
  of muscle, 134
Lactose, 55
  inversion of, 332
Lævulose, 54
Lardacein, 46
Larynx, movements of, 429
Latent period of involuntary muscle, 149
  of voluntary muscle, 105
Lecithin, 49
Leucine, 34, 333
Leucocytes, chemistry of, 73
  emigration of, 281
  formation of, 73
    of fibrin ferment from, 82
  varieties of, 60
Liver, secretion of, 338
  formation of urea in, 438, 481
    of glycogen in, 354, 490
    of sugar in, 490, 492
Lungs, circulation in, 422

[illegible] Oct 4

Lungs, gaseous interchanges in, 386-401
Lymph, 286-297
Lymph-flow in plethora, 283
Lysine, 36

MALTASE, 304, 336
Maltose, 54
Manometer, Hurthle's, 216
  max. and min., 217
  mercurial, 193
Marey's law, 251
Mastication, 368
Menstruation, 687
Metabolism of carbohydrates, 489–496
  of fat, 485–488
  of proteins, 443, 478–484
Methæmoglobin, 64
Micturition, 467–472
Milk, coagulation of, 324
  composition of, 508
  secretion of, 691
Milk-sugar, 55
Millon's reaction, 38
Mono-saccharides, 51
Motor centres, 657
  tracts in brain, 627
    cord, 598
Mucins, 45
Mucoids, 46
Müller's law, [illegible]4, 518
Muscle, 14, 87 *et seq*
  absolute force of, 107
  action of constant current on, 97
    of drugs on, 142
  chemical changes in activity, 135
  chemistry of, 131
  contraction of, 102
  decomposition of creatin in, 441
  direct excitability of, 95
  effect of temperature on, 140
  electrical changes in, 119
  excitation of, 95
  extensibility of, 111
  fatigue of, 141
  gaseous interchanges of, 138
  heat-production in, 114
  isometric contraction of, 108
  isotonic contraction of, 107
Muscle, latent period of, 105, 149
  mechanical efficiency of, 117
  proteins of, 131
  secondary contraction of, 130
  source of energy of, 137
  structure of, 87
  tone of, 608
  unstriated, physiology of, 149-156
    structure of, 89
  voluntary contraction of, 145
  work of, 113
Muscle-plasma, 131
Muscle-sound, 145
Muscles of frog's leg, 93
Muscular actions, co-ordination of, 643
  energy, source of, 497
  mechanisms of digestion, 363-376
    of micturition, 469
    of respiration, 377
Muscular sense, 531
  tone, 608
Myogen, 132
Myographs, 103–105
Myohæmatin, 133
Myopia, 559
Myosin, 132

NEGATIVE variation, 122
Negativity, 125
Nerve, 159–188
  conduction in, 169
  degeneration in, 584
  double conduction in, 163
  effect of injury on, 179
  electrical change in, 164
  excitation of, 167, 171, 174
  excitation of human, 173
  fatigue in, 177, 188
  heat-formation in, 165
  influence of temperature on, 179
    drugs on, 180
  polarisation phenomena in, 182
  propagation in, 162
  retrograde degeneration of, 5
  structure of, 160
Nerve-cell, function of, 591, 680
  structure of, 588
Nerve-cells of cord, 594
Nerve-centres in medulla, 641

- Nerve-degeneration, influence on vaso-constrictors, 269
- Nerve-roots, 20, 582, 603
- Nerves, cranial, 634–640
  - depressor, 272
  - pelvic, 374, 470
  - pilomotor, 474, 674
  - pressor, 272
  - secretory, to salivary glands, 313
    - to stomach, 326
  - splanchnic, action on blood-pressure, 267
    - on intestine, 367
    - origin of, 677
  - vagus, *see* Vagi
  - vaso-dilator, 268
  - vaso-motor, 260, 266
  - visceral, 21, 670
- Nervi erigentes, 268
- Nervous impulse, 162
  - nature of, 18, 187
  - system, 16, 582–681
    - visceral, 669–684
- Neuroglia, 592
- Neurokeratin, 47
- Neuron, 590
- Nissl's granules, 591
- Nitrogen, assimilation of, 26, 478
- Nitrogenous equilibrium, 483
- *Nœud vital*, 402
- Nucleic acid, 43
- Nuclein, 42
- Nucleo-proteins, 42
  - injection of, 82

- Œdema, inflammatory, 281
- Olfactory sense, 541
- Oncometer, 262
- Ophthalmometer, 554
- Ornithine, 36
- Osazones, 52
- Osmotic pressure, definition, 464
- Oxidation in tissues, 396
  - mechanism of, 28
- Oxydases, 29
- Oxygen, influence of changes in tension, 407, 419
  - intramolecular, 139
- Oxyhæmoglobin, *see* Hæmoglobin
- Oxyproline, 36, 333

- Pain, 529
- Pancreas, 328
  - sugar-function of, 495
- Pancreatic fistula, 329
  - juice, action of, 331–337, 353
- Paradoxical contraction, 186
- Parathyroids, 519
- Parturition, 689
- Pelvic nerve, action on colon, 374
  - on bladder, 470
- Pepsin, 325
- Peptone-plasma, 83
- Peptones, 42
  - properties of, 320
- Phagocytes, 281
- Phakoscope, 553
- Phenyl-alanine, 36, 332
- Phloridzin, action of, 493
- Photohæmatachometer, 203
- Pigments of bile, 343
  - of urine, 452
- Pilomotor nerves, 474, 673
- Pineal gland, 519
- Pituitary body, 519
- Plasma, blood, 58
  - muscle, 131
- Plasmine, 79
- Plethora, 283
  - hydræmic, 294
- Polarisation, 119
  - in nerve, 182
- Polypeptides, 37, 335
- Poly-saccharides, 55
- Presbyopia, 560
- Pressor nerves, 272
- Proline, 36, 333
- Protamines, 36
- Proteins, absorption of, 355
  - chemistry of, 31–47
  - classification of, 38
  - conjugated, 42
  - crystallisation of, 32
  - disintegration of, 33
  - halogen derivatives of, 40
  - metabolism of, 443, 478–484
  - of milk, 508
  - of muscle, 131
  - pancreatic digestion of, 332
  - requirements of man, 483
  - tests for, 37
- Prothrombin, 81
- Protoplasm, definition, 5

- Pseudo-globulin, 76
- Ptyalin, 304, 305
- Pulse, 196, 223
- Purine bases, 449

- REACTION, 15
  - time, 606
- Recurrent sensibility, 587
- Reflex action, 17, 606, 642
  - in peripheral ganglia, 683
- Refractory period, 240
- Remak's ganglion, 235
- Rennin, 304, 323
- Reproduction, 685–693
- Respiration, 12, 377–427
  - chemistry of, 386–401
  - cutaneous, 476
  - internal, 14
  - nervous mechanism of, 402
  - of muscle, 136
- Respiratory quotient, 138, 387
  - undulations in blood-pressure, 423
  - interchange of gases, 386–401
- Retina, functions of, 563
  - structure of, 561
- Retractor penis, 149
- Rheochord, 704
- Rheoscopic frog, 130
- Rheotome, 128
- Rhythm of unstriated muscle, 150
- Ribs, movements of, 380
- Rigor mortis, 138
- Rods, 562, 565

- SALIVA, 305–315
- Salts, absorption of, 356
  - of urine, 451
- Sarcolactic acid in muscle, 133
- Sarcomere, 90
- Sarcoplasm, 90
- Sarcosine, 36
- Sarcostyle, 90
- Sebaceous glands, 473
- Secretin, 330, 341
- Secretion, histological changes during, 308, 325
  - paralytic, 315
  - relation to lymph production, 291
  - salivary, 307
- Secretory nerves, to pancreas, 330
  - to salivary glands, 313
  - to stomach, 326
- Semicircular canals, functions of, 535
- Sensation, 522
  - auditory, 544
  - cortical representation of, 660
  - cutaneous, 526
  - gustatory, 539
  - olfactory, 541
  - muscular, 531
  - paths in brain, 631
    - in cord, 603
  - static, 534
  - temperature, 528
  - visual, 570
- Senses, 522–581
- Sensory areas, 660
- Serine, 32
- Skin, functions of, 473–477
  - sensory functions of, 526
- Smell, 541
- Soaps, 49
- Speech, 428
- Sphygmographs, 224
- Spinal cord, 20, 582–611
  - nerve cells of, 594
  - paths of impulses in, 603
  - reflex functions of, 606
  - structure and tracts of, 582–602
  - white matter of, 596
  - roots, degeneration of, 586
- Splanchnic nerves, action on blood-pressure, 267
  - on intestine, 367
  - origin of, 677
- Spleen, 513
  - functions of, 515
  - relation to blood-formation, 72
- 'Staircase' phenomenon, 239
- Stannius' ligature, 235
- Starch, 55
- Static sense, 534
- Steapsin, 304, 331
- Stomach, digestion in, 316
  - movements of, 365
- Stroma, 58
  - chemistry of, 67
- 'Stromuhr,' 201
- Succus entericus, 347

- Sugar of milk, 55
- Sugars, chemistry of, 51–56
- Summation in heart-muscle, 239
  - of contractions, 110
  - of stimuli, 151, 606
- Suprarenal capsules, 520
- Sweat, secretion of, 474
- Sympathetic ganglia, effect of nicotine on, 266, 683
  - nerves to heart, 245, 248
  - system, 21, 670
    - vaso-constrictor action of, 266

- Tambour, 216
- Tactile sensations, 526
- Taste, 539
- Taurocholic acid, 842
- Tears, secretion of, 579
- Temperature, regulation of, 501
  - sense, 528
- Tendon phenomena, 609
- Tension, influence on heart-muscle, 239
  - of gases in blood, 392
- Tetanus, 111
- Thermopile, 115
- Thrombin, 80
- Thrombogen, 82
- Thrombokinase, 82
- Thrombus, formation of, 83
- Thymus gland, 516
- Thyroid gland, 517
- Traube-Hering curves, 277
- Trypsine, 304, 331-335
- Tryptophane, 36, 333
- Tyrosine, 34, 334

- Urea, 435
  - origin of, 437–443
- Uric acid, 444-449
- Urine, composition of, 434
  - nitrogenous constituents of, 435–453
  - pigments of, 452
  - salts of, 451
- Urine, secretion of, 454–466
- Urobilin, 69, 452
- Urochrome, 452

- Vagi, action on bronchi, 418
    - on heart, 247
    - on intestines, 372
    - on œsophagus, 365
    - on respiration, 409–418
    - on stomach, 367
  - cardiac branches of, 246
  - functions of, 640
  - secretory fibres of, 330
- Vascular mechanism, 189–285
  - system, capacity of, 199
- Vaso-dilator nerves, 268
- Vaso-motor impulses in cord, 605
  - nerves, 260
    - course of, 266
- Veins, extensibility of, 191
  - pressure in, 192
  - pulse in, 232
  - structure of, 190
  - velocity in, 204
- Ventilation, 421
- Veratrine, 142
- Visceral nerves, 21, 670
  - nervous system, 670–684
- Vision, 550–580
  - binocular, 567
  - colour, 572
  - stereoscopic, 579
- Voice, production of, 431
- Voluntary contraction, 145
- Vomiting, 369
- Vowel sounds, 431

- Work of heart, 253
  - of muscle, 113

- Xanthoproteic reaction, 38

- Zymogen, 311
  - in pancreas, 331
  - in stomach, 325

PRINTED BY
SPOTTISWOODE AND CO LTD, NEW-STREET SQUARE
LONDON

No. 3.

MARCH, 1907.

J. & A. CHURCHILL

Recent Works for Students and Practitioners of Medicine.

LONDON:
7, Great Marlborough Street.

INDEX.

PAGE
2 Anatomy. Physiology.
3 Materia Medica. Pharmacy.
4 Hygiene. Bacteriology.
5 Pathology. Psychology. Dictionaries.
6 Medicine.
7 Medicine.
8 Surgery.
9 Surgery. Anæsthetics.
10 Neurology. Urinary Disorders.
11 Midwifery. Gynæcology. Medical Jurisprudence.
12 Ophthalmology.
13 Otology. Pædiatrics. Dentistry.
14 Tropical Diseases. Dermatology.
15 Chemistry. Physics.
16 Microscopy Miscellaneous.

FREE ON . . .
APPLICATION.

1. Complete Catalogue.
2. Catalogue of Science Books.

Anatomy & Physiology

Human Anatomy: a Treatise by various Authors. Edited by Henry Morris, M A, M B Lond., F R C S, Surgeon to, and Lecturer on Surgery at, the Middlesex Hospital Third Edition 846 Illustrations, of which 267 are in several colours 30s net

Anatomical Terminology, with Special Reference to the B N.A By Llewellys F Barker, M D, Professor of Medicine, Johns Hopkins University, Baltimore. With Illustrations and 2 Coloured Plates 5s net

A Manual of Practical Anatomy. By the late Professor Alfred W Hughes, M B, M C Edin, Professor of Anatomy, King's College, London Edited and completed by Arthur Keith, M D, Lecturer on Anatomy, London Hospital Medical College In three parts, Part I, 10s 6*d* Part II, 8s 6*d* Part III, 10s 6*d*

Heath's Practical Anatomy: a Manual of Dissections. Edited by J E Lane, F R C S, Surgeon and Lecturer on Anatomy at St Mary's Hospital Ninth Edition 321 Engravings 12s 6*d*

Clinical Applied Anatomy; or, The Anatomy of Medicine and Surgery By Charles R Box, M D, F R C P Lond, Physician to Out-patients, St Thomas's Hospital, and W McAdam Eccles, M S Lond, F R C S Eng, Assistant Surgeon, St Bartholomew's Hospital Illustrated by 45 Plates, of which 12 are coloured, and 6 Figures in the Text 12s 6*d* net

Essentials of Surface Anatomy. By Charles R. Whittaker, L R C S, L.R C P, etc, Demonstrator of Anatomy, Surgeons' Hall, Edinburgh 2s 6*d* net

Text-Book of Anatomy for Nurses. By Elizabeth R Bundy, M D, Member of the Medical Staff of the Woman's Hospital of Philadelphia With a Glossary and 191 Illustrations, 34 of which are printed in colours 7s 6*d* net

Human Osteology. By Luther Holden. Eighth Edition. Edited by Charles Stewart, F R.S, and Robert W. Reid, M D, F R C S. 59 Lithographic Plates and 74 Engravings 16s

BY THE SAME AUTHOR

Landmarks, Medical and Surgical. Fourth Edition. 3s 6*d*

Elements of Human Physiology. By Ernest H. Starling, M D, F R C P, F R S, Jodrell Professor of Physiology in University College, London Seventh Edition 321 Illustrations 12s net.

An Introduction to Physiology. By L. A. Hodgkinson Lack, M B, Ch B 8s net

Physiological Chemistry. A Text-book for Students and Practitioners By Charles E Simon, M D, late Resident Physician, Johns Hopkins Hospital, Baltimore Second Edition 14s net

Materia Medica ❧ Pharmacy

A Text-Book of Materia Medica for Students of Medicine By C R Marshall, M D, Professor of Materia Medica and Therapeutics in the University of St. Andrews 127 Illustrations 10*s* 6*d* net

Materia Medica, Pharmacy, Pharmacology, and Therapeutics By W Hale White, M D, F R C P, Physician to, and Lecturer on Medicine at, Guy's Hospital Ninth Edition 6*s* 6*d* net

Southall's Organic Materia Medica. Edited by John Barclay, B Sc Lond Sixth Edition 7*s* 6*d*

An Introduction to the Study of Materia Medica. By Henry G Greenish, F I C, F L S, Professor of Pharmaceutics to the Pharmaceutical Society 213 Illustrations 15*s*

BY THE SAME AUTHOR,

The Microscopical Examination of Foods and Drugs, in the Entire, Crushed, and Powdered States 168 Illustrations. 10*s* 6*d* net

ALSO, WITH EUGENE COLLIN,

An Anatomical Atlas of Vegetable Powders. 138 Illustrations 12*s* 6*d* net

Practical Pharmacy. By E. W. Lucas, F.I C., F C.S. 283 Illustrations 12*s* 6*d*

The National Standard Dispensatory. By H A. Hare, B Sc, M D, and others 478 Illustrations 31*s* 6*d* net

Medical and Pharmaceutical Latin for Students of Pharmacy and Medicine By Reginald R Bennett, Pharmacist and Teacher of Pharmacy at University College Hospital, London 6*s* net

A Companion to the British Pharmacopœia. By Peter Wyatt Squire, F L S, F C S Seventeenth Edition 12*s* 6*d*

BY THE SAME AUTHOR

Pocket Companion to the British Pharmacopœia. Leather, 7*s* 6*d* net

ALSO

The Pharmacopœias of thirty of the London Hospitals Arranged in Groups for Comparison Seventh Edition 6*s*

The Pharmaceutical Formulary: a Synopsis of the British and Foreign Pharmacopœias By Henry Beasley Twelfth Edition by J Oldham Braithwaite 6*s* 6*d*

BY THE SAME AUTHOR

The Druggist's General Receipt Book. Tenth Edition. 6*s* 6*d*

The Book of Prescriptions (Beasley) with an Index of Diseases and Remedies Rewritten by E W Lucas, F I C, F C S Eighth Edition 5*s* net

Tuson's Veterinary Pharmacopœia. Sixth Edition. Edited by James Bayne, F C S 7*s* 6*d* net

Year-Book of Pharmacy. Annually, 10*s*

Hygiene ❧ Bacteriology

The Theory and Practice of Hygiene. By J. Lane Notter, M D, late Professor of Hygiene in the Army Medical School, and W H Horrocks, M B, B Sc, Assistant Professor of Military Hygiene in the Staff Medical College Second Edition 15 Plates and 134 other Illustrations 25s

Manual of Hygiene. By W. H. Hamer, M D, Lecturer on Public Health, St Bartholomew's Hospital, Assistant Medical Officer of Health of the County of London 93 Illustrations 12s 6d net

A Handbook of Hygiene and Sanitary Science. By Geo Wilson, M A, M D, Medical Officer of Health for Mid-Warwickshire. Eighth Edition. Illustrated 12s 6d

The Effects of Borax and Boric Acid on the Human System Third Treatise With Diagrams By Dr. Oscar Liebreich 5s net

A Simple Method of Water Analysis, especially designed for the use of Medical Officers of Health By John C Thresh, M D Vic, D Sc.Lond Fifth Edition, enlarged 2s 6d

BY THE SAME AUTHOR

The Examination of Waters and Water Supplies. 19 Plates and 11 Figures in the Text 14s net

ALSO, WITH ARTHUR E PORTER, M D, M.A CANTAB

Preservatives in Food and Food Examination. 8 Plates 14s net

A Manual of Bacteriology, Clinical and Applied. By Richard T Hewlett, M D, Professor of General Pathology and Bacteriology in King's College, London Second Edition 20 Plates and 66 Figures in the Text 12s 6d

BY THE SAME AUTHOR

Serum Therapy, Bacterial Therapeutics, and Vaccines 20 Figures 5s net

Clinical Diagnostic Bacteriology, including Serum- and Cyto-diagnosis By Alfred C Coles, M D, D Sc, F R S E 2 Coloured Plates 8s net

A Text-Book of Bacteriology for Students and Practitioners of Medicine By G M Sternberg, M D, Surgeon-General, U S Army Second Edition 9 Plates and 198 Figures in the Text 26s

An Introduction to the Bacteriological Examination of Water. By W H Horrocks, M B, B Sc Lond 10s 6d

Lessons in Disinfection and Sterilisation. By F W Andrewes, M D, F.R C P, Lecturer on Pathology, St Bartholomew's Hospital 31 Illustrations 3s net

Pathology & Psychology Dictionaries

Pathology, General and Special, for Students of Medicine By R Tanner Hewlett, M D, F R C P, D P H, Professor of General Pathology and Bacteriology in King's College, London 28 Plates and 13 Illustrations in Text Post 8vo 10s 6*d* net.

A Manual of General or Experimental Pathology, for Students and Practitioners By W S Lazarus-Barlow, M D, F R C P, Director of the Cancer Research Laboratories, Middlesex Hospital, Second Edition 21s net

BY THE SAME AUTHOR

The Elements of Pathological Anatomy and Histology for Students 24s net

Surgical Pathology and Morbid Anatomy. By Anthony A Bowlby, F R C S, Surgeon to St Bartholomew's Hospital Fourth Edition 186 Engravings 10s 6*d*

The Pathologist's Handbook: a Manual for the Post-mortem Room By T N Kelynack, M D 126 Illustrations Pegamoid, 4s 6*d*

Psychological Medicine. By Maurice Craig, M.A., M.D, F R C P, Physician and Lecturer on Mental Diseases, Guy's Hospital 22 Plates 12s 6*d* net

Mental Diseases: Clinical Lectures. By T. S. Clouston, M D, F.R C P Edin, Lecturer on Mental Diseases in the University of Edinburgh Sixth Edition 30 Plates 14s net

The Mental Affections of Children: Idiocy, Imbecility, and Insanity By Wm W Ireland, M D Edin Second Edition 21 Plates 14s

The Force of Mind; or, the Mental Factor in Medicine By Alfred T Schofield, M D, Hon Physician to Friedenheim Hospital Third Edition 5s net

BY THE SAME AUTHOR

Unconscious Therapeutics; or, The Personality of the Physician Second Edition 5s net

ALSO

The Management of a Nerve Patient. 5*s* net.

The Journal of Mental Science. Published Quarterly, by Authority of the Medico-Psychological Association 5s

A German-English Dictionary of Terms used in Medicine and the Allied Sciences By Hugo Lang, B A, and Bertram Abrahams, M B, B Sc, F R C P 15s net

Dunglison's Dictionary of Medical Science. By Thomas L Stedman, M D Twenty-third Edition 577 Illustrations, including 84 page-plates 34s net

A Medical Vocabulary: an explanation of Terms and Phrases used in Medical Science, their Derivation, Meaning, Application, and Pronunciation By R G Mayne, M D, LL D Seventh Edition, by W W Wagstaffe, B A, F R C S, and G D Parker, M B 12s 6*d*

Medicine

A Text-Book of Medicine. Begun by the late C. Hilton Fagge, M D , completed and re-written by P H Pye-Smith, M D , F R S Fourth Edition 2 vols 42*s*

Manual of the Practice of Medicine. By Frederick Taylor, M D , F R C P , Physician to, and Lecturer on Medicine at, Guy's Hospital Seventh Edition Illustrated 15*s* net

A System of Clinical Medicine for Practitioners and Students By Thos D Savill, M D , M R C P In 2 vols 4 Coloured Plates, and 286 Figures in the Text Vol I Local Diseases and Pyrexial Disorders, 12*s* 6*d* net , Vol II Diseases of the Skin, the Nervous System, etc , 8*s* 6*d* net

A Short Practice of Medicine. By Robert A. Fleming, M A , M D , F R C P E , F R S E , Lecturer on Practice of Medicine, School of the Royal Colleges, Edinburgh , Assistant Physician, Royal Infirmary, Edinburgh Illustrated, partly in colour 10*s* 6*d* net

The Practice of Medicine. By M. Charteris, M D., Professor of Therapeutics and Materia Medica in the University of Glasgow. Eighth Edition Edited by F J Charteris, M B , Ch B Illustrated 10*s*

Student's Guide to Medical Diagnosis. By Samuel Fenwick, M D , F R C P , and W Soltau Fenwick, M D , B S Ninth Edition 139 Engravings 9*s*

Text-Book of Medical Treatment (Diseases and Symptoms) By Nestor I C Tirard, M D , F R C P , Professor of the Principles and Practice of Medicine, King's College, London 15*s*

A Manual of Family Medicine and Hygiene for India Published under the Authority of the Government of India By Sir William J Moore, K C I E , M D Seventh Edition edited by Major J H Tull Walsh, I.M S 70 Engravings 6*s* net

The Blood : how to Examine and Diagnose its Diseases By Alfred C Coles, M D , D.Sc , F R S Edin Third Edition 7 Coloured Plates 10*s* 6*d* net

Lectures on Medicine to Nurses. By Herbert E. Cuff, M D , F R C S , Medical Superintendent, North-Eastern Fever Hospital, London Fourth Edition 29 Illustrations 3*s* 6*d*

How to Examine the Chest. By Samuel West, M D , F R C P , Physician to St Bartholomew's Hospital Third Edition 46 Engravings 5*s*

Medicine

Ulcer of the Stomach and Duodenum. By Samuel Fenwick, M D , F R C P , and W Soltau Fenwick, M.D , B S 55 Illustrations 10s. 6d

BY THE SAME AUTHORS.

Cancer and other Tumours of the Stomach. 70 Illustrations. 10s 6d

On Carbohydrate Metabolism, with an Appendix on the Assimilation of Carbohydrate into Proteid and Fat, followed by the Fundamental Principles and the Treatment of Diabetes dialectically discussed. By Frederick W Pavy, M D , LL D , F R S , F R C P., Consulting Physician to Guy's Hospital With 8 Plates 6s net

The Schott Methods of the Treatment of Chronic Diseases of the Heart, with an account of the Nauheim Baths, and of the Therapeutic Exercises By W Bezly Thorne, M D , M R C P Fifth Edition Illustrated 5s net

The Clinical Examination of Urine, with an Atlas of Urinary Deposits By Lindley Scott, M A , M D 41 original Plates (mostly in colours) 15s net

Urinary Examination made easy. By T. Carruthers, M B , Ch B 1s 6d net

Some Disorders of the Spleen. By Frederick Taylor, M D , F R C P , Physician to, and Lecturer on Medicine at, Guy's Hospital 8s net

Rational Organotherapy, with Reference to Urosemiology Translated from the Russian Text by Professor Dr. A von Poehl, Professor Prince J von Tarchanoff, Dr Alf von Poehl, and Dr. P Wachs Vol I 7s 6d net

On Gallstones, or Cholelithiasis. By E M. Brockbank, M D Vict , M R C P Lond , Honorary Physician to the Ancoats Hospital, Manchester 7s

Obstinate Hiccough: the Physiology, Pathology, and Treatment. By L F B Knuthsen, M D Edin 6s

On Syphonage and Hydraulic Pressure in the Large Intestine, with their Bearing upon the Treatment of Constipation, Appendicitis, etc By Ralph Winnington Leftwich, M D 3s net

Uric Acid as a Factor in the Causation of Disease By Alexander Haig, M D , F R C P , Physician to the Metropolitan Hospital Sixth Edition 75 Illustrations 15s

BY THE SAME AUTHOR

Uric Acid, an Epitome of the Subject. Second Edition. 2s 6d net

ALSO

Diet and Food considered in relation to Strength and Power of Endurance, Training, and Athletics Sixth Edition 2s net

Surgery

The Operations of Surgery: intended for use on the Dead and Living Subject alike By W H A Jacobson, M Ch Oxon, F.R C S, Surgeon Guy's Hospital, and F J Steward, M S Lond, F.R C S, Assistant Surgeon, Guy's Hospital Fourth Edition 2 vols. 550 Illustrations 42s

Surgery: its Theory and Practice. By William J Walsham, F R C S, Surgeon to St Bartholomew's Hospital • Ninth Edition, by W G Spencer, F R C S, Surgeon to the Westminster Hospital 620 Engravings (including 24 Skiagrams) 18s net

The Operative Surgery of Malignant Disease. By Henry T Butlin, F R C S, Surgeon to St Bartholomew's Hospital. Second Edition. 12 Engravings 14s

Surgical Pathology and Morbid Anatomy. By Anthony A Bowlby, F R C S, Surgeon to St Bartholomew's Hospital Fourth Edition 186 Engravings 10s 6*d*

A Manual of Surgical Diagnosis. By James Berry, B S Lond, F R C S, Surgeon to, and Lecturer on Surgery at, the Royal Free Hospital 6s net

A Synopsis of Surgery. By R. F Tobin, Surgeon to St Vincent's Hospital, Dublin Second Edition Interleaved, leather binding 6s 6*d*

Heath's Manual of Minor Surgery and Bandaging. Thirteenth Edition Revised by Bilton Pollard, F R C S, Surgeon to University College Hospital 198 Engravings 6s net

BY THE SAME AUTHOR

Injuries and Diseases of the Jaws. Fourth Edition. Edited by Henry Percy Dean, M S, F R C S, Assistant Surgeon to the London Hospital. 187 Wood Engravings 14s

ALSO

Clinical Lectures on Surgical Subjects delivered at University College Hospital. First Series, 6s, Second Series, 6s

An Essay on the General Principles of the Treatment of Spinal Curvatures By R Heather Bigg Illustrated by Photographs and Sketches 5s net

Surgery & Anæsthetics

The Surgery of the Alimentary Canal. By Alfred Ernest Maylard, M B Lond and B S, Senior Surgeon to the Victoria Infirmary, Glasgow 27 Swantype Plates and 89 Figures in the Text 25*s*

BY THE SAME AUTHOR

A Student's Handbook of the Surgery of the Alimentary Canal 97 Illustrations 8*s* 6*d*

ALSO

Abdominal Pain: its Causes and Clinical Significance Second Edition 7*s* 6*d* net

Clinical Essays and Lectures. By Howard Marsh, F R C S, Professor of Surgery in the University of Cambridge 26 Illustrations 7*s* 6*d*

Ovariotomy and Abdominal Surgery. By Harrison Cripps, F R C S, Surgical Staff, St Bartholomew's Hospital Numerous Plates. 25*s*

Diseases of the Thyroid Gland and their Surgical Treatment By James Berry, B S Lond, F R C S, Surgeon to the Royal Free Hospital 121 Illustrations 14*s*

Hare-lip and Cleft Palate. By R. W. Murray, F.R C S, Surgeon, David Lewis Northern Hospital 25 Illustrations 3*s*

Modern Bullet-Wounds and Modern Treatment, with Special Regard to Long Bones and Joints, Field Appliances and First Aid By Major F Smith, D S O, R A M C 3*s* net

Surgical Emergencies. By Paul Swain, F R.C.S., Surgeon to the South Devon and East Cornwall Hospital Fifth Edition 149 Engravings 6*s*

The Accessory Sinuses of the Nose. By A Logan Turner, M D Edin, Surgeon for Diseases of the Ear and Throat, Deaconess Hospital, Edinburgh 81 Illustrations 12*s* net

On the Development and Anatomy of the Prostate Gland By W G Richardson, M B, B S, F R C S, Assistant Surgeon at the Royal Infirmary, Newcastle-on-Tyne Heath Scholarship Prize Essay 47 Plates 10*s* 6*d* net

Chloroform: a Manual for Students and Practitioners By Edward Lawrie, M B Edin, Lieut-Col I M S, Residency Surgeon, Hyderabad Illustrated 5*s* net

A Guide to Anæsthetics for the Student and General Practitioner By Thomas D Luke, M B F R C S, Edinburgh Third Edition 43 Engravings 5*s* net

Neurology & Urinary Disorders

Paralysis and other Nervous Diseases in Childhood and Early Life By James Taylor, M D, F R C P, Physician National Hospital for Paralysed and Epileptic, Queen Square 74 Illustrations 12*s* 6*d* net

A Manual of Diseases of the Nervous System.

By Sir William R Gowers, M D, F R S

Vol. I.—**Nerves and Spinal Cord.** Third Edition, by the Author and James Taylor, M D, F R C P 192 Engravings 15*s*

BY THE SAME AUTHOR

Clinical Lectures on Diseases of the Nervous System 7*s* 6*d*

ALSO

Subjective Sensations of Sight and Sound, Abiotrophy, and other Lectures on Diseases of the Nervous System 18 Illustrations 6*s* net

ALSO

Epilepsy and Other Chronic Convulsive Diseases: their Causes, Symptoms, and Treatment Second Edition 10*s* 6*d*

Text-Book of Nervous Diseases for Students and Practitioners of Medicine By Charles L Dana, M D Fourth Edition 246 Illustrations 20*s*

The Treatment of Nervous Disease. By J. J G Brown, M D, Assistant Physician, Royal Infirmary of Edinburgh 15*s* net

Selected Papers on Stone, Prostate, and other Urinary Disorders By Reginald Harrison, F R C S, Surgeon to St Peter's Hospital 15 Illustrations 5*s*

Obscure Diseases of the Urethra. By E. Hurry Fenwick, F R C S, Surgeon to the London Hospital 63 Illustrations 6*s* 6*d*.

BY THE SAME AUTHOR

Obscure Diseases of the Kidney, the Value of Ureteric Meatoscopy in their Diagnosis and Treatment 14 Plates and 43 Figures in the Text 6*s* 6*d*

ALSO

Operative and Inoperative Tumours of the Urinary Bladder 39 Illustrations 5*s* net

ALSO

Tumours of the Urinary Bladder. Fasc. I. 5*s* net.

ALSO

Ulceration of the Bladder, Simple, Tuberculous, and Malignant a Clinical Study Illustrated 5*s*

ALSO

A Handbook of Clinical Cystoscopy. 31 Plates and 144 Figures in the Text 18*s* net

ALSO

Atlas of Electric Cystoscopy. 34 Coloured Plates. 21*s* net

Midwifery & Gynæcology
Medical Jurisprudence

Manual of Midwifery, including all that is likely to be required by Students and Practitioners. By Alfred L. Galabin, M.A., M.D., F.R.C.P., Consulting Obstetric Physician to Guy's Hospital. Sixth Edition. 329 Engravings. 14s. net.

Manual of Midwifery. By T. W. Eden, M.D., C.M. Edin., F.R.C.P. Lond., Assistant Obstetric Physician and Lecturer on Practical Midwifery, Charing Cross Hospital. 26 Plates and 283 Illustrations in the Text. 10s. *6d.* net.

A Short Practice of Midwifery, embodying the Treatment adopted in the Rotunda Hospital, Dublin. By Henry Jellett, M.D., B.A.O. Dub., Ex-Assistant Master, Rotunda Hospital. Fourth Edition. 152 Illustrations. 8s. *6d.*

BY THE SAME AUTHOR.

A Short Practice of Midwifery for Nurses, with a Glossary of the Medical Terms used in the Book. Second Edition. 4 Coloured Plates and 134 Illustrations. 6s. *6d.* net.

A Short Manual for Monthly Nurses. By Charles J. Cullingworth, M.D., F.R.C.P., Obstetric Physician to St. Thomas's Hospital, and M. A. Atkinson, Matron of the General Lying-in Hospital, Lambeth. Fifth Edition. 1s. *6d.*

Diseases of Women. By Alfred L. Galabin, M.A., M.D., F.R.C.P., Consulting Obstetric Physician to Guy's Hospital. Sixth Edition. 284 Engravings. 16s. net.

A Short Practice of Gynæcology. By Henry Jellett, M.D., B.A.O. Dub., Ex-Assistant Master, Rotunda Hospital, Dublin. Second Edition. 225 Illustrations. 10s. *6d.*

Outlines of Gynæcological Pathology and Morbid Anatomy. By C. Hubert Roberts, M.D. Lond., Physician to the Samaritan Free Hospital for Women. 151 Illustrations. 21s.

Lectures on Medical Jurisprudence and Toxicology. By Fred J. Smith, M.D., F.R.C.P., Lecturer on Forensic Medicine and Toxicology at the London Hospital. 7s. *6d.*

Medical Jurisprudence: its Principles and Practice. By Alfred S. Taylor, M.D., F.R.C.P., F.R.S. Fifth Edition, by Fred J. Smith, M.D., F.R.C.P., Lecturer on Medicine at the London Hospital. 2 vols. 39 Engravings. 36s. net.

Ophthalmology

Nettleship's Diseases of the Eye. Sixth Edition. Revised and Edited by W T Holmes Spicer, M B , F R C S , Ophthalmic Surgeon to St Bartholomew's Hospital 161 Engravings 8*s* 6*d*

Medical Ophthalmoscopy: A Manual and Atlas. Fourth Edition By Sir W R Gowers, M D , F R S , and Marcus Gunn, M B , F R C S , Surgeon to the Royal London Ophthalmic Hospital Autotype Plates and Woodcuts 14*s* net

Manual of Ophthalmic Surgery and Medicine. By W H H Jessop, M A , F R C S , Ophthalmic Surgeon to St Bartholomew's Hospital 5 Coloured Plates and 110 Woodcuts 9*s* 6*d*

Practical Handbook of Diseases of the Eye. By D Chalmers Watson, M B , Ophthalmic Physician, Marshall Street Dispensary, Edinburgh Second Edition 9 Coloured Plates and 31 Figures in the Text 5*s* net

Diseases of the Eye. By Cecil Edward Shaw, M.D., M Ch , Ophthalmic Surgeon to the Ulster Hospital for Children and Women, Belfast With a Test-Card for Colour Blindness 3*s* 6*d*

Refraction of the Eye: a Manual for Students. By Gustavus Hartridge, F R C S , Surgeon to the Royal Westminster Ophthalmic Hospital Fourteenth Edition 109 Illustrations, also Test-types, etc 5*s* net

BY THE SAME AUTHOR

The Ophthalmoscope: a Manual for Students. Fourth Edition 65 Illustrations and 4 Plates 4*s* 6*d*

Ocular Therapeutics according to the most Recent Discoveries. By Dr A Darier Translated by Sydney Stephenson, M B , C M , Ophthalmic Surgeon to the Evelina Hospital and the North-Eastern Hospital for Children 10*s* 6*d* net

Elementary Ophthalmic Optics, including Ophthalmoscopy and Retinoscopy By J Herbert Parsons, B S , B Sc , F R C S , Curator, Royal London Ophthalmic Hospital 66 Illustrations 6*s* 6*d*

Royal London Ophthalmic Hospital Reports. By the Medical and Surgical Staff Vol XVI, Part IV 5*s* net

Ophthalmological Society of the United Kingdom Transactions Vol XXVI 12*s* 6*d* net

Otology ∅ Pædiatrics ∅ Dentistry

Some Points in the Surgical Anatomy of the Temporal Bone from Birth to Adult Life By ARTHUR H CHEATLE, F R C S, Aural Surgeon to King's College Hospital 112 Illustrations 5s net

Diseases of the Ear, including the Anatomy and Physiology of the Organ, together with the Treatment of the Affections of the Nose and Pharynx By T MARK HOVELL, Senior Aural Surgeon to the London Hospital Second Edition 128 Engravings 21s

The Diseases of Children. By JAMES F. GOODHART, M D, F R C P, and G F STILL, M D, F R C P, Professor of the Diseases of Children, King's College Eighth Edition 12s 6d net

The Wasting Diseases of Infants and Children. By EUSTACE SMITH, M D, F R C P, Physician to the King of the Belgians, and to the East London Hospital for Children Sixth Edition 6s

On the Natural and Artificial Methods of Feeding Infants and Young Children By EDMUND CAUTLEY, M D, Physician to the Belgrave Hospital for Children Second Edition 7s 6d

Dental Anatomy, Human and Comparative: a Manual By CHARLES S TOMES, M A, F R S Sixth Edition 286 Engravings 12s 6d net

BY THE SAME AUTHOR

A System of Dental Surgery. By Sir JOHN TOMES, F R S Revised by C S TOMES, M A, F R S, and WALTER S. NOWELL, M A Oxon Fifth Edition 318 Engravings 15s net

Practical Treatise on Mechanical Dentistry. By JOSEPH RICHARDSON, M D, D D S Seventh Edition, revised and edited by GEORGE W WARREN, D D S, 690 Engravings 22s

Decay in Teeth: an Investigation into its Cause and Prevention By J SIM WALLACE, M D, D Sc, L D S R C S Second Edition 5s

A Manual of Dental Metallurgy. By ERNEST A SMITH, Assay Office, Sheffield Second Edition 38 Illustrations 6s 6d

Dental Materia Medica, Pharmacology, and Therapeutics By CHARLES W GLASSINGTON, M R C S, L D S Edin, Senior Dental Surgeon, Westminster Hospital 6s

Tropical Diseases & Dermatology

The Malarial Fevers of British Malaya. By HAMILTON WRIGHT, M D (MCGILL), Director of the Institute for Medical Research, Federated Malay States Map and Charts 3s net

BY THE SAME AUTHOR

The Etiology and Pathology of Beri-Beri. With Map and Charts 3s net

Beri-Beri: its Symptoms and Symptomatic Treatment By PERCY N GERRARD, M.D, District Surgeon, Federated Malay States Civil Service 2s 6d net

BY THE SAME AUTHOR

Extracts from the above. 1s 6d. net.

On the Causes and Continuance of Plague in Hong Kong, with Suggestions as to Remedial Measures, a Report presented to the Secretary of State for the Colonies By W J SIMPSON, M D, F R C P Numerous Charts and Diagrams 10s net

On the Outbreak of Yellow Fever in British Honduras in 1905, together with an Account of the Distribution of the Stegomyia fasciata in Belize, and the Measures necessary to Stamp Out or Prevent the Occurrence of Yellow Fever, a Report presented to the Government of that Colony By RUBERT BOYCE, M B, F R S Illustrated with numerous Plates and Plans Folio 3s 6d net

A Handbook on Leprosy. By S P IMPEY, M D, late Chief and Medical Superintendent, Robben Island Leper and Lunatic Asylums, Cape Colony 38 Plates 12s

A Manual of Diseases of the Skin, with an Analysis of 20,000 Consecutive Cases and a Formulary By DUNCAN E BULKLEY, M D, New York Fourth Edition. 6s 6d

Skin Diseases of Children. By GEO. H. FOX, M.D, Clinical Professor of Diseases of the Skin, College of Physicians and Surgeons, New York 12 Photogravure and Chromographic Plates and 60 Illustrations in the Text 12s 6d

On Maternal Syphilis, including the Presence and Recognition of Syphilitic Pelvic Disease in Women By JOHN A SHAW-MACKENZIE, M D Coloured Plates 10s 6d

The Diagnosis and Treatment of Syphilis. By TOM ROBINSON, M D St And, Physician to the Western Skin Hospital Second Edition. 3s 6d

BY THE SAME AUTHOR

The Diagnosis and Treatment of Eczema. Second Edition 3s 6d

Ringworm, and some other Scalp Affections: their Cause and Cure By HAYDN BROWN, L.R C P Ed. 5s

Chemistry & Physics

Chemistry, Inorganic and Organic. By CHARLES L BLOXAM Ninth Edition, by J M THOMSON, F R S, Professor of Chemistry in King's College, London, and A G BLOXAM, F I C 284 Engravings 18s net

The Elements of Chemistry. By M. M. PATTISON MUIR, M A, Fellow of Caius College, Cambridge Illustrated 10s 6d net

The Analyst's Laboratory Companion: a Col-lection of Tables and Data for Chemists and Students By A E JOHNSON, B Sc, F I C Third Edition 6s 6d net

Commercial Organic Analysis: a Treatise on the Properties, Modes of Assaying, Proximate Analytical Examination, etc, of Organic Chemicals and Products used in the Arts, Manufactures, etc In 7 vols By A H ALLEN, F I C [Prospectus on application]

Volumetric Analysis; or, the Quantitative Esti-mation of Chemical Substances by Measure By FRANCIS SUTTON, F.C S, F.I C Ninth Edition 121 Engravings 20s net

A Manual of Chemistry, Theoretical and Prac-tical By WILLIAM A TILDEN, D Sc, F R S, Professor of Chemistry in the Royal College of Science, London 2 Plates and 143 Woodcuts 10s

Valentin's Practical Chemistry and Qualitative and Quantitative Analysis Edited by Dr W R HODGKINSON, F R S E, Professor of Chemistry at the Royal Military Academy, Woolwich Ninth Edition Engravings, 9s. (The Tables separately, 2s 6d)

A Handbook of Physics and Chemistry for the Conjoint Board By H E CORBIN, B Sc Lond, and A. M STEWART, B Sc Lond Third Edition 165 Illustrations 6s 6d. net

A Treatise on Physics. By ANDREW GRAY, LL D, F.R S., Professor of Natural Philosophy in the University of Glasgow Vol I Dynamics and Properties of Matter 350 Illustrations 15s

Practical Chemistry and Qualitative Analysis. By FRANK CLOWES, D Sc Lond, Professor of Chemistry in the University Coll, Nottingham Seventh Edition. 101 Engravings 8s 6d

Quantitative Analysis. By FRANK CLOWES, D.Sc Lond., and J B COLEMAN, A R C Sci Dub, Professor of Chemistry, South-West London Polytechnic Seventh Edition 125 Engravings 10s

BY THE SAME AUTHORS

Elementary Practical Chemistry. Fifth Edition

Part I General Chemistry 75 Engravings 2s 6d net
Part II Analytical Chemistry 20 Engravings 2s 6d net

ntroduction to Chemical Analysis. By HUGH C H. CANDY, B A, B Sc, F I C, Lecturer on Chemistry in the London Hospital Medical College, Analyst to the London Hospital 3s 6d net

Researches on the Affinities of the Elements and on the Causes of the Chemical Similarity or Dissimilarity of Elements and Compounds By GEOFFREY MARTIN, B Sc Lond Illustrated 16s net

Microscopy & Miscellaneous

The Microscope and its Revelations. By the late William B Carpenter, C.B, M D, LL D, F R S Eighth Edition, by the Rev W H Dallinger, LL D, F R S 23 Plates and more than 800 Wood Engravings 28s Half-Calf 32s, or, in two vols, sold separately, cloth, 14s each

Vol I. The Microscope and its Accessories

Vol II The Microscope, its Revelations

The Microtomist's Vade-Mecum: a Handbook of the Methods of Microscopic Anatomy By Arthur Bolles Lee Sixth Edition 15s net

The Quarterly Journal of Microscopical Science. Edited by E. Ray Lankester, M A, LL D, F R S Each Number, 10s net

Manual of Botany, in two Vols. By J Reynolds Green, Sc D, M A, F R S, Professor of Botany to the Pharmaceutical Society

Vol I Morphology and Anatomy Third Edition 778 Engravings 7s 6*d*

Vol II Classification and Physiology Second Edition 466 Engravings. 10s

BY THE SAME AUTHOR

An Introduction to Vegetable Physiology. 184 Illustrations 10s 6*d*

Therapeutic Electricity and Practical Muscle Testing By W S Hedley, M D, in charge of the Electro-therapeutic Department of the London Hospital 110 Illustrations. 8s 6*d*

A Handbook of Medical Climatology. By S. Edwin Solly, M D., M R C S, late President of the American Climatological Association Engravings and Coloured Plates 16s

Nursing, General, Medical, and Surgical, with an Appendix on Sickroom Cookery By Wilfred J Hadley, M D, F.R C P, Physician to the London Hospital 3s 6*d*

About Dreaming, Laughing, and Blushing. By Sir Arthur Mitchell, K C B 5s net

St. Thomas's Hospital Reports. By the Medical and Surgical Staff. Vol XXXIII New Series 8s 6*d* net

Guy's Hospital Reports. By the Medical and Surgical Staff Vol XLV Third Series 10s 6*d* net

Encyclopædia Medica. Edited by Chalmers Watson, M B, M R C P E In 14 Volumes £13 12s net

LONDON

J. & A. CHURCHILL

7 GREAT MARLBOROUGH STREET